



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07K 14/00	A2	(11) International Publication Number: WO 00/37491 (43) International Publication Date: 29 June 2000 (29.06.2000)
(21) International Application Number: PCT/IB99/02058 (22) International Filing Date: 20 December 1999 (20.12.1999) (30) Priority Data: 60/113,686 22 December 1998 (22.12.1998) US 60/141,032 25 June 1999 (25.06.1999) US (60) Parent Application or Grant GENSET [/]; (). BOUGUELERET, Lydie [/]; (). DUMAS, Jean-Baptiste [/]; (). DUCLERT, Aymeric [/]; (). BOUGUELERET, Lydie [/]; (). DUMAS, Jean-Baptiste [/]; (). DUCLERT, Aymeric [/]; (). GENSET ; ().		Published
(54) Title: COMPLEMENTARY DNA'S ENCODING PROTEINS WITH SIGNAL PEPTIDES (54) Titre: ADN COMPLEMENTAIRES CODANT POUR DES PROTEINES SECRETEES AVEC DES PEPTIDES SIGNAUX (57) Abstract <p>The sequences of cDNAs encoding secreted proteins are disclosed. The cDNAs can be used to express secreted proteins or fragments thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The cDNAs may also be used to design expression vectors and secretion vectors.</p> (57) Abrégé <p>L'invention concerne des séquences d'ADNc codant pour des protéines sécrétées. Les cADN peuvent servir pour exprimer des protéines sécrétées ou des fragments de celles-ci ou à obtenir des anticorps capables précisément de se lier auxdites protéines. Les cADN peuvent également servir dans des opérations de diagnostic, de médecine légale, de thérapie génique et de mappage des chromosomes. On peut également les utiliser pour concevoir des vecteurs d'expression et des vecteurs de sécrétion.</p>		

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(54) Title: COMPLEMENTARY DNA'S ENCODING PROTEINS WITH SIGNAL PEPTIDES (57) Abstract The sequences of cDNAs encoding secreted proteins are disclosed. The cDNAs can be used to express secreted proteins or fragments thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The cDNAs may also be used to design expression vectors and secretion vectors.		

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Description

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COMPLEMENTARY DNA'S ENCODING PROTEINS WITH SIGNAL PEPTIDES

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced. Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained, *i.e.*, labeling non-coding DNA as coding DNA and vice versa.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding fragments of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify cDNAs which include sequences adjacent to the EST sequences. The cDNAs may contain all of the sequence of the EST which was used to obtain them or only a fragment of the sequence of the EST which was used to obtain them. In addition, the cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the cDNAs may include fragments of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, these short EST sequences were often obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs (Adams *et al.*, *Nature* 377:3-174, 1996, Hillier *et al.*, *Genome Res.* 6:807-828, 1996). In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region (5'UTR) of the mRNA from which the cDNA is derived. Indeed, 5'UTRs have been shown to affect either the stability or translation of

5 mRNAs. Thus, regulation of gene expression may be achieved through the use of alternative 5'UTRs as shown, for instance, for the translation of the tissue inhibitor of metalloprotease mRNA in mitogenically activated cells (Waterhouse *et al.*, *J Biol Chem.* 265:5585-9, 1990). Furthermore, modification of 5'UTR through mutation, insertion or translocation events may even be implied in pathogenesis. For instance, the
10 5 fragile X syndrome, the most common cause of inherited mental retardation, is partly due to an insertion of multiple CGG trinucleotides in the 5'UTR of the fragile X mRNA resulting in the inhibition of protein synthesis via ribosome stalling (Feng *et al.*, *Science* 268:731-4, 1995). An aberrant mutation in regions of the 5'UTR known to inhibit translation of the proto-oncogene *c-myc* was shown to result in upregulation of *c-myc* protein levels in cells derived from patients with multiple myelomas (Willis *et al.*, *Curr Top Microbiol Immunol*
15 224:269-76, 1997). In addition, the use of oligo-dT primed cDNA libraries does not allow the isolation of complete 5'UTRs since such incomplete sequences obtained by this process may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs.

20 Moreover, despite the great amount of EST data that large-scale sequencing projects have yielded (Adams *et al.*, *Nature* 377:174, 1996, Hillier *et al.*, *Genome Res.* 6:807-828, 1996), information concerning the biological function of the mRNAs corresponding to such obtained cDNAs has revealed to be limited. Indeed, whereas the knowledge of the complete coding sequence is absolutely necessary to investigate the biological function of mRNAs, ESTs yield only partial coding sequences. So far, large-scale full-length cDNA
25 cloning has been achieved only with limited success because of the poor efficiency of methods for constructing full-length cDNA libraries. Indeed, such methods require either a large amount of mRNA (Ederly *et al.*, 1995), thus resulting in non representative full-length libraries when small amounts of tissue are available or require PCR amplification (Maruyama *et al.*, 1994; CLONTECHniques, 1996) to obtain a reasonable number of clones, thus yielding strongly biased cDNA libraries where rare and long cDNAs are
30 lost. Thus, there is a need to obtain full-length cDNAs, *i.e.* cDNAs containing the full coding sequence of their corresponding mRNAs.

35 While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding
40 genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and may be responsible for producing a clinically relevant response in their target cells. In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- α , interferon- β ,
45 interferon- γ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and multiple sclerosis. For
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5 these reasons, cDNAs encoding secreted proteins or fragments thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

10 In addition to being therapeutically useful themselves, secretory proteins include short peptides, 5 called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by 15 operably linking the signal sequences to a gene encoding the protein for which secretion is desired. In addition, fragments of the signal peptides called membrane-translocating sequences, may also be used to direct the intracellular import of a peptide or protein of interest. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cells in which it is 20 produced. Signal sequences encoding signal peptides also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. 25 Thus, there exists a need to identify and characterize the 5' fragments of the genes for secretory proteins which encode signal peptides.

Sequences coding for secreted proteins may also find application as therapeutics or diagnostics. In particular, such sequences may be used to determine whether an individual is likely to express a detectable 30 phenotype, such as a disease, as a consequence of a mutation in the coding sequence for a secreted protein. In instances where the individual is at risk of suffering from a disease or other undesirable phenotype as a result of a mutation in such a coding sequence, the undesirable phenotype may be corrected by introducing a normal coding sequence using gene therapy. Alternatively, if the undesirable phenotype results from overexpression of the protein encoded by the coding sequence, expression of the protein may 35 be reduced using antisense or triple helix based strategies. 25

The secreted human polypeptides encoded by the coding sequences may also be used as therapeutics by administering them directly to an individual having a condition, such as a disease, resulting from a mutation in the sequence encoding the polypeptide. In such an instance, the condition can be cured 40 or ameliorated by administering the polypeptide to the individual.

30 In addition, the secreted human polypeptides or fragments thereof may be used to generate antibodies useful in determining the tissue type or species of origin of a biological sample. The antibodies may also be used to determine the cellular localization of the secreted human polypeptides or the cellular 45 localization of polypeptides which have been fused to the human polypeptides. In addition, the antibodies may also be used in immunoaffinity chromatography techniques to isolate, purify, or enrich the human polypeptide or a target polypeptide which has been fused to the human polypeptide. 35

50 Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of

isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross *et al.*, *Nature Genetics* 6: 236-244, 1994). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock *et al.*, *Genome Res.* 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity and of comprehensiveness. Thus, there exists a need to identify and systematically characterize the 5' fragments of the genes.

cDNAs including the 5' ends of their corresponding mRNA may be used to efficiently identify and isolate 5'UTRs and upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA (Theil *et al.*, *BioFactors* 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, cDNAs containing the 5' ends of secretory protein genes may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5' coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant cDNAs which encode secreted proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Such cDNAs will be referred herein as "full-length" cDNAs. Alternatively, the cDNAs may contain a fragment of the open reading frame. Such cDNAs will be referred herein as "ESTs" or "5'ESTs". In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a fragment of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the cDNA of the present invention. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10^4 - 10^6 fold purification of the native message.

Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules.

Thus, cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant cDNAs" as defined herein. Likewise, cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant cDNAs" as defined herein. However, cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant cDNAs."

The term "polypeptide" refers to a polymer of amino acids without regard to the length of the polymer; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide. This term also does not specify or exclude post-expression modifications of polypeptides, for example, polypeptides which include the covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term polypeptide. Also included within the definition are polypeptides which contain one or more analogs of an amino acid (including, for example, non-naturally occurring amino acids, amino acids which only occur naturally in an unrelated biological system, modified amino acids from mammalian systems etc.), polypeptides with substituted linkages, as well as other modifications known in the art, both naturally occurring and non-naturally occurring.

As used interchangeably herein, the terms "nucleic acids," "oligonucleotides," and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form. The term "nucleotide" as used herein as an adjective to describe molecules comprising RNA, DNA, or RNA/DNA hybrid sequences of any length in single-stranded or duplex form. The term "nucleotide" is also used herein as a noun to refer to individual nucleotides or varieties of nucleotides, meaning a molecule, or individual unit in a larger nucleic acid molecule, comprising a purine or pyrimidine, a ribose or deoxyribose sugar moiety, and a phosphate group, or phosphodiester linkage in the case of nucleotides within an oligonucleotide or polynucleotide. Although the term "nucleotide" is also used herein to encompass "modified nucleotides" which comprise at least one modifications (a) an alternative linking group, (b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar, for examples of analogous linking groups, purine, pyrimidines, and sugars see for example PCT publication No. WO 95/04064. The polynucleotide sequences of the invention may be prepared by any known method, including synthetic, recombinant, *ex vivo* generation, or a combination thereof, as well as utilizing any purification methods known in the art.

The terms "base paired" and "Watson & Crick base paired" are used interchangeably herein to refer to nucleotides which can be hydrogen bonded to one another by virtue of their sequence identities in a manner like that found in double-helical DNA with thymine or uracil residues linked to adenine residues by two hydrogen bonds and cytosine and guanine residues linked by three hydrogen bonds (See Stryer, L., *Biochemistry*, 4th edition, 1995).

The terms "complementary" or "complement thereof" are used herein to refer to the sequences of polynucleotides which are capable of forming Watson & Crick base pairing with another specified polynucleotide throughout the entirety of the complementary region. For the purpose of the present invention, a first polynucleotide is deemed to be complementary to a second polynucleotide when each base in the first polynucleotide is paired with its complementary base. Complementary bases are, generally, A and T (or A and U), or C and G. "Complement" is used herein as a synonym from "complementary polynucleotide," "complementary nucleic acid" and "complementary nucleotide sequence". These terms are applied to pairs of polynucleotides based solely upon their sequences and not any particular set of conditions under which the two polynucleotides would actually bind. Preferably, a "complementary" sequence is a sequence which an A at each position where there is a T on the opposite strand, a T at each position where there is an A on the opposite strand, a G at each position where there is a C on the opposite strand and a C at each position where there is a G on the opposite strand.

"Stringent", "moderate," and "low" hybridization conditions are as defined below.

In particular, the present invention relates to cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble

5 proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal peptides which direct the extracellular secretion of the proteins encoded by the cDNAs.

10 5 Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-
15 translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the cell membrane.

20 The cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to
15 express fragments of the secreted protein. The fragments may comprise the signal peptides encoded by the cDNAs or the mature proteins encoded by the cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The fragments may also comprise polypeptides having at least 5, 10, 15, 20, 25, 30, 35, 40,
25 50, 75, 100, or 150 consecutive amino acids encoded by the cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the cDNAs or
20 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the
35 signal peptides encoded by the cDNAs may also be obtained.

25 In some embodiments, the cDNAs include the signal sequence. In other embodiments, the cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the
40 proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the cDNA in which thymidine residues in the sequence of the cDNA are replaced by uracil residues in the mRNA.

35 45 50 The cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from

5 abnormal expression of the genes corresponding to the cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

10 The present invention also relates to secretion vectors capable of directing the secretion of a protein of interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

15 The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the cDNAs such as promoters or upstream regulatory sequences.

20 In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

25 One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 24-73 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

30 Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 8 consecutive bases of the sequence of one of SEQ ID NOs: 24-73 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 consecutive bases of one of the sequences of SEQ ID NOs: 24-73 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

35 Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 24-73 or a sequence complementary to one of the sequences of SEQ ID NOs: 24-73. In one aspect of this embodiment, the nucleic acid is recombinant.

40 Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 24-73, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

45 A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

50 Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

55 Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 74-123.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 74-123.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 74-123.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 74-123.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 5 or 8 consecutive amino acids of one of the sequences of SEQ ID NOs: 74-123. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 consecutive amino acids of one of the sequences of SEQ ID NOs: 74-123.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 74-123.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 74-123.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 74-123, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 24-73, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 74-123, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 24-73 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 24-73 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 24-73, wherein the full coding sequence comprises the sequence encoding the signal peptide and the sequence encoding the mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode a mature protein which are described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode the signal peptide which are described herein.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 74-123. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 74-123.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 24-73, or one of the sequences complementary to the sequences of SEQ ID NOs: 24-73, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 24-73, the sequences complementary to the sequences of SEQ ID NOs: 24-73, or 20 fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 24-73, the sequences complementary to the sequences of SEQ ID NOs: 24-73, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in an ECACC deposit, which contains the sequences of SEQ ID NOs. 25-40 and 42-46, having an accession No. 99061735 and named SignalTag 15061999 or deposited in an ECACC deposit having an accession No. 98121805 and named SignalTag 166-191, which contains SEQ ID NOs.: 47-73, or a fragment of these nucleic acids comprising a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in an ECACC deposit, which contains the sequences of SEQ ID NOs. 25-40 and 42-46, having an accession No. 99061735 and named SignalTag 15061999 or deposited in an ECACC deposit having an accession No. 98121805 and named SignalTag 166-191, which contains SEQ ID NOs.: 47-73, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 amino acids of

5 SEQ ID NOs: 74-123, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 10 to 13. Also encompassed by the invention are purified polynucleotides encoding said polypeptides.

10 Another embodiment of the present invention is a computer readable medium having stored thereon a sequence selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123.

15 Another embodiment of the present invention is a computer system comprising a processor and a data storage device wherein the data storage device has stored thereon a sequence selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123. In some 20 embodiments the computer system further comprises a sequence comparer and a data storage device having reference sequences stored thereon. For example, the sequence comparer may comprise a computer program which indicates polymorphisms. In other aspects of the computer system, the system further comprises an identifier which identifies features in said sequence.

25 Another embodiment of the present invention is a method for comparing a first sequence to a reference sequence wherein the first sequence is selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123 comprising the steps of reading the first sequence and the reference sequence through use of a computer program which compares sequences and determining differences between the first sequence and the reference sequence with the computer program. In some aspects of this embodiment, said step of determining differences between the first sequence and 30 the reference sequence comprises identifying polymorphisms.

35 Another embodiment of the present invention is a method for identifying a feature in a sequence selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123 comprising the steps of reading the sequence through the use of a computer program which identifies features in sequences and identifying features in the sequence with said computer program.

25 Brief Description of the Drawings

Figure 1 is a table with all of the parameters that can be used for each step of cDNA analysis.

40 Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

30 Figure 3 provides a diagram of a RT-PCR-based method to isolate cDNAs containing sequences adjacent to 5'ESTs used to obtain them

45 Figure 4 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 5 describes the transcription factor binding sites present in each of these promoters.

35 Figure 6 is a block diagram of an exemplary computer system.

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Figure 7 is a flow diagram illustrating one embodiment of a process 200 for comparing a new nucleotide or protein sequence with a database of sequences in order to determine the homology levels between the new sequence and the sequences in the database.

Figure 8 is a flow diagram illustrating one embodiment of a process 250 in a computer for determining whether two sequences are homologous.

Figure 9 is a flow diagram illustrating one embodiment of an identifier process 300 for detecting the presence of a feature in a sequence.

Figure 10 illustrates an alignment of the protein of SEQ ID NO: 76, encoded by the cDNA SEQ ID NO: 26 with the parotid HPSP protein (SEQ ID NO: 124).

Figure 11 illustrates an alignment of the protein of SEQ ID NO: 93, encoded by the cDNA SEQ ID NO: 43 with a human transmembrane protein (SEQ ID NO: 125). The conserved cysteines are in bold. The conserved region around the second cysteine is underlined. The potential active site QxVxG is in italics.

Figure 12 illustrates an alignment of the protein of SEQ ID NO: 75, encoded by the cDNA SEQ ID NO: 25 with a human putative sialyltransferase (SEQ ID NO: 126), displaying 89.4% identical residues in a 301 amino acid overlap. The sialylmotifS is in bold. The sialylmotifL is in italics. The potential transmembrane segments are underlined.

Figure 13 illustrates an alignment of the protein of SEQ ID NO: 104, encoded by the extended cDNA SEQ ID NO: 54, with the murine recombination activating gene 1 inducing protein (SEQ ID NO: 177).

Detailed Description of the Preferred Embodiment

1. Obtaining cDNA libraries including the 5'Ends of their Corresponding mRNAs

The cDNAs of the present invention may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such cDNAs are referred to herein as "full length cDNAs." Alternatively, the cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

The methods explained therein can also be used to obtain cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the cDNAs. In some embodiments, the cDNAs isolated using these methods encode at least 5 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 24-73. In further embodiments, the cDNAs encode at least 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 consecutive amino acids of the proteins encoded by the sequences of SEQ ID NOs: 24-73. In a preferred embodiment, the cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 24-73.

The cDNAs of the present invention were obtained from cDNA libraries derived from mRNAs having intact 5' ends as described in Examples 1 to 5 using either a chemical or enzymatic approach.

EXAMPLE 1

Preparation of mRNA

5 Total human RNAs or polyA⁺ RNAs derived from different tissues were respectively purchased from LABIMO and CLONTECH and used to generate cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczynski and Sacchi, *Analytical Biochemistry* 162:156-159, 1987). PolyA⁺ RNA was isolated from total
10 RNA (LABIMO) by two passes of oligo dT chromatography, as described by Aviv and Leder, *Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the polyA⁺ RNAs were checked. Northern blots hybridized with a probe corresponding to an ubiquitous mRNA, such as elongation factor 1 or elongation factor 2, were used
15 to confirm that the mRNAs were not degraded. Contamination of the polyA⁺ mRNAs by ribosomal sequences was checked using Northern blots and a probe derived from the sequence of the 28S rRNA. Preparations of mRNAs with less than 5% of rRNAs were used in library construction. To avoid constructing
20 libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed fungal mRNAs was examined using PCR.

EXAMPLE 2

Methods for Obtaining mRNAs having Intact 5' Ends

15 Following preparation of the mRNAs from various tissues as described above, selection of mRNA with intact 5' ends and specific attachment of an oligonucleotide tag to the 5' end of such mRNA is performed using either a chemical or enzymatic approach. Both techniques take advantage of the presence of the "cap" structure, which characterizes the 5' end of intact mRNAs and which comprises a guanosine
20 generally methylated once, at the 7 position.

The chemical modification approach involves the optional elimination of the 2', 3'-cis diol of the 3' terminal ribose, the oxidation of the 2', 3', -cis diol of the ribose linked to the cap of the 5' ends of the mRNAs into a dialdehyde, and the coupling of the dialdehyde to a derivatized oligonucleotide tag. Further detail
35 regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in International Application No. WO96/34981, published November 7, 1996.

The enzymatic approach for ligating the oligonucleotide tag to the 5' ends of mRNAs with intact 5' ends involves the removal of the phosphate groups present on the 5' ends of uncapped incomplete mRNAs, the subsequent decapping of mRNAs with intact 5' ends and the ligation of the phosphate present at the 5' end of the decapped mRNA to an oligonucleotide tag. Further detail regarding the enzymatic approaches for
40 obtaining mRNAs having intact 5' ends are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EP0 625572 and Kato *et al.*, *Gene* 150:243-250 (1994).

In either the chemical or the enzymatic approach, the oligonucleotide tag has a restriction enzyme
45 site (e.g. EcoRI sites) therein to facilitate later cloning procedures. Following attachment of the oligonucleotide tag to the mRNA, the integrity of the mRNA was then examined by performing a Northern blot using a probe complementary to the oligonucleotide tag.

EXAMPLE 3

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using either the chemical or the enzymatic method, first strand cDNA synthesis was performed using reverse transcriptase with an oligo-dT primer or random nonamer. In some instances, this oligo-dT primer contained an internal tag of at least 4 nucleotides which is different from one tissue to the other. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

The second strand of the cDNA was then synthesized with a Klenow fragment using a primer corresponding to the 5' end of the ligated oligonucleotide. Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

EXAMPLE 4

Cloning of cDNAs derived from mRNA with intact 5' ends into BlueScript

Following second strand synthesis, the cDNAs were cloned into the phagemid pBlueScript II SK-vector (Stratagene). The ends of the cDNAs were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only hemi-methylated site, hence the only site susceptible to EcoRI digestion. In some instances, to facilitate subcloning, an Hind III adaptor was added to the 3' end of cDNAs.

The cDNAs were then size fractionated using either exclusion chromatography (AcA, Biosepra) or electrophoretic separation which yields 3 or 6 different fractions. The cDNAs were then directionally cloned either into pBlueScript using either the EcoRI and SmaI restriction sites or the EcoRI and Hind III restriction sites when the Hind III adaptor was present in the cDNAs. The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

EXAMPLE 5

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

Clones containing the oligonucleotide tag attached to cDNAs were then selected as follows.

The plasmid DNAs containing cDNA libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang *et al.*, *Gene* 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry *et al.*, *Biotechniques*, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide tag described in example 2. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated

5 magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into
10 bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP.

15 II. Characterization of the 5' Ends of Clones

10 In order to sequence only cDNAs which contain the 5' ends of their corresponding mRNA, a first round of sequencing was performed on the 5' end of clones as described in example 6. In some instances, only a partial sequence of the clone, therein referred to as "5'EST" was obtained. In other instances, the
20 complete sequence of the clone, herein referred to as a "cDNA" is obtained. A computer analysis was then performed on the 5' ESTs or cDNAs as described in Examples 7 and 8 in order to evaluate the quality of the
15 cDNA libraries and in order to select clones containing sequences of interest among cDNAs which contain the 5' ends of their corresponding mRNA.

25 EXAMPLE 6

Sequencing of The 5'End of cDNA Clones

The 5' ends of cloned cDNAs were then sequenced as follows. Plasmid inserts were first amplified
20 by PCR on PE 9600 thermocyclers (Perkin-Elmer, Applied Biosystems Division, Foster City, CA) using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer). Sequencing reactions were performed using PE 9600 thermocyclers with standard dye-primer chemistry and
35 ThermoSequenase (Amersham Pharmacia Biotech). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with ethanol, resuspended in
30 formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data obtained from the sequencing of 5' ends of all cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were
35 performed. A proprietary base-caller, working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or fewer bases having more than 4
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suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the sequences. However, the resulting sequences may contain 1 to 5 nucleotides belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Following sequencing as described above, the sequences of the cDNA clones were entered in a database for storage and manipulation as described below. Before searching the cDNA clones in the database for sequences of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated, namely, endogenous contaminants (ribosomal RNAs, transfer RNAs, mitochondrial RNAs) and exogenous contaminants (prokaryotic RNAs and fungal RNAs) using software and parameters described in Figure 1. In addition, cDNA sequences showing homology to repeated sequences (Alu, L1, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats) were identified and masked in further processing.

EXAMPLE 7

Determination of Efficiency of 5' End Selection

To determine the efficiency at which the above selection procedures isolated cDNAs which include the 5' ends of their corresponding mRNAs, the sequences of 5'ESTs or cDNAs were aligned with a reference pool of complete mRNA/cDNA extracted from the EMBL release 57 using the FASTA algorithm. The reference mRNA/cDNA starting at the most 5' transcription start site was obtained, and then compared to the 5' transcription start site position of the 5'EST or cDNA. More than 75% of 5'ESTs or cDNAs had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA sequences available in the EMBL database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of 5'ESTs or cDNAs including the authentic 5' ends of their corresponding mRNAs.

EXAMPLE 8

Identification of Open Reading Frames Coding For Potential Signal Peptides

The obtained nucleic acid sequences were then screened to identify those having uninterrupted open reading frames (ORF) with a good coding probability using proprietary software. When the full-length cDNA was obtained, only complete ORFs, namely nucleic acid sequences beginning with a start codon and ending with a stop codon, longer than 150 nucleotides were considered. When only 5'EST sequences were obtained, both complete ORFs longer than 150 nucleotides and incomplete ORFs, namely nucleic acid sequences beginning with a start codon and extending up to the end of the 5'EST, longer than 60 nucleotides were considered.

The retrieved ORFs were then searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, *Nucleic Acids Res.* 14:4683-4690, 1986. Those 5'ESTs or cDNA sequences encoding a polypeptide with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5'ESTs or cDNAs which matched a known

human mRNA or EST sequence and had a 5' end more than 30 nucleotides downstream of the known 5' end were excluded from further analysis.

EXAMPLE 9

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino acids located at the N terminus of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in figure 2.

Using the above method of identification of secretory proteins, 5' ESTs of the following polypeptides known to be secreted were obtained: human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs or cDNAs actually functions as a signal peptide, the signal sequences from the 5' ESTs or cDNAs may be cloned into a vector designed for the identification of signal peptides. Such vectors are designed to confer the ability to grow in selective medium only to host cells containing a vector with an operably linked signal sequence. For example, to confirm that a 5' EST or cDNA encodes a genuine signal peptide, the signal sequence of the 5' EST or cDNA may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors with the correctly inserted 5' EST or cDNA signal sequence confirms that the 5' EST or cDNA encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the 5'ESTs or cDNAs into expression vectors such as pXT1 as described below, or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from control cells containing vectors lacking the signal sequence or cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

EXAMPLE 10

Evaluation of Expression Levels and Patterns of mRNAs Corresponding to 5' ESTs or cDNAs

5 The spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs or cDNAs, as well as their expression levels, may be determined. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be
10 discussed in more detail below.

In addition, cDNAs or 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a cDNA or 5' EST. By comparing mRNA
15 expression patterns and quantities in samples taken from healthy individuals with those from individuals suffering from a particular disease, cDNAs and 5' ESTs responsible for the disease may be identified.

Expression levels and patterns of mRNAs corresponding to 5' ESTs or cDNAs may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA
20 polymerase promoter to produce antisense RNA. Preferably, the 5' EST or cDNA is 100 or more nucleotides in length. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The
25 unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the
35 serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain
40 the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

35 A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived
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from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or cDNAs to determine which 5' ESTs or cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), cDNAs, 5' ESTs or fragments of the full length cDNAs, cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena *et al.* (*Science* 270:467-470, 1995; *Proc. Natl. Acad. Sci. U.S.A.* 93:10614-10619, 1996). Full length cDNAs, cDNAs, 5' ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu *et al.* (*Genome Research* 6:492-503, 1996). The full length cDNAs, cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or cDNAs can be done through high density nucleotide arrays as described by Lockhart *et al.* (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky *et al.* (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or cDNAs are synthesized directly on the chip (Lockhart *et al.*, *supra*) or synthesized and then addressed to the chip (Sosnowski *et al.*, *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart *et al.*, *supra* and application of different electric fields (Sosnowsky *et al.*, Proc. Natl. Acad. Sci. 94:1119-1123), the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or cDNA from which the oligonucleotide sequence has been designed.

III. Characterization of cDNAs including the 5' End of their Corresponding mRNA

EXAMPLE 11

Characterization of the complete sequence of cDNA clones

Clones which include the 5' end of their corresponding mRNA and which encode a new protein with a signal peptide as determined in the aforementioned procedure were then fully sequenced as follows.

First, both 5' and 3' ends of cloned cDNAs were sequenced twice in order to confirm the identity of the clone using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer. Second, primer walking was performed if the full coding region had not been obtained yet using software such as OSP to choose primers and automated computer software such as ASMG (Sutton *et al.*, *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag. Contigation was then performed using 5' and 3' sequences and eventually primer walking sequences. The sequence was considered complete when the resulting contigs included the full coding region as well as overlapping sequences with vector DNA on both ends. In addition, clones were entirely sequenced in order to obtain at least two sequences per clone. Preferably, the sequences were obtained from both sense and antisense strands. All the contigated sequences for each clone were then used to obtain a consensus sequence which was then submitted to the computer analysis described below.

Alternatively, clones which include the 5' end of their corresponding mRNA and which encode a new protein with a signal peptide, as determined in the aforementioned procedure, may be subcloned into an appropriate vector such as pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) before full sequencing.

EXAMPLE 12

Determination of Structural and Functional Features

Following identification of contaminants and masking of repeats, structural features, e.g. polyA tail and polyadenylation signal, of the sequences of cDNAs were subsequently determined using the algorithm, parameters and criteria defined in figure 1. Briefly, a polyA tail was defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search was restricted to the last 100 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. To search for a polyadenylation signal, the polyA tail was clipped from the full-length sequence. The 50 bp preceding the polyA tail were searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors as well as known variation in the canonical sequence of the polyadenylation signal.

Functional features, e.g. ORFs and signal sequences, of the sequences of cDNAs were subsequently determined as follows. The 3 upper strand frames of cDNAs were searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 80 amino acids were preferred. Each found ORF was then scanned for the presence of a signal peptide using the matrix method described in example 10.

Sequences of cDNAs were then compared, on a nucleotidic or proteic basis, to public sequences available at the time of filing.

EXAMPLE 13

Selection of Full Length Sequences

cDNAs that had already been characterized by the aforementioned computer analysis were then submitted to an automatic procedure in order to preselect cDNAs containing sequences of interest.

a) Automatic sequence preselection

All cDNAs clipped for vector on both ends were considered. First, a negative selection was performed in order to eliminate sequences which resulted from either contaminants or artifacts as follows. Sequences matching contaminant sequences were discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats. Sequences lacking polyA tail were also discarded. Those cDNAs which matched a known human mRNA or EST sequence and had a 5' end more than 30 nucleotides downstream of the known 5' end were also excluded from further analysis. Only ORFs ending before the polyA tail were kept.

Then, for each remaining cDNA containing several ORFs, a preselection of ORFs was performed using the following criteria. The longest ORF was preferred. If the ORF sizes were similar, the chosen ORF was the one which signal peptide had the highest score according to Von Heijne method as defined in Example 10.

Sequences of cDNA clones were then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides were clustered in the same class. Each cluster was then subjected to a clustal analysis that detects sequences resulting from internal priming or from alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis served as a basis for manual selection of the sequences.

b) Manual sequence selection

Manual selection was carried out using automatically generated reports for each sequenced cDNA clone. During the manual selection procedure, a selection was performed between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class were aligned and compared. If the homology between nucleotide sequences of clones belonging to the same class was more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class was more than 80% over 20 amino acid stretches, then the clones were considered as being identical. The chosen ORF was either the one exhibiting matches with known amino acid sequences or the best one according to the criteria mentioned in the automatic sequence preselection section. If the nucleotide and amino acid homologies were less than 90% and 80% respectively, the clones were said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length cDNA clones encoding sequences of interest was performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal, eventually matches with public ESTs in 5' or 3' of the sequence) were first checked in order to confirm that the cDNA was complete in 5' and in 3'. Then, homologies with known nucleic acids and proteins were examined in order to determine whether the clone sequence matched a known nucleic acid or protein sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there was no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence included substantial new information, such as encoding a protein resulting from alternative splicing of an mRNA coding for an already known protein, the sequence was kept. Examples of such cloned full length cDNAs containing sequences of interest are described in Example 14. Sequences resulting from chimera or double inserts as assessed by homology to other sequences were discarded during this procedure.

EXAMPLE 14Characterization of Full-length cDNAs

The procedure described above was used to obtain or full length cDNAs derived from a variety of tissues. The following list provides a few examples of thus obtained cDNAs.

Using this procedure, the full length cDNA of SEQ ID NO:1 (internal identification number 108-005-5-0-F9-FLC) was obtained. This cDNA encodes a potentially secreted protein (SEQ ID NO:2) with a signal peptide having a von Heijne score of 4.1.

Using this procedure, the full length cDNA of SEQ ID NO:3 (internal identification number 108-004-5-0-G10-FLC) was obtained. This cDNA encodes a potentially secreted protein (SEQ ID NO:4) with a signal peptide having a von Heijne score of 5.3.

Using this procedure, the full length cDNA of SEQ ID NO:5 (internal identification number 108-004-5-0-B12-FLC) was obtained. This cDNA encodes a potentially secreted protein (SEQ ID NO:6) with a signal peptide having a von Heijne score of 7.0.

Using this procedure, the full length cDNA of SEQ ID NO:7 (internal identification number 108-013-5-O-G5-FLC) was obtained. This cDNA encodes a potentially secreted protein (SEQ ID NO:8) with a signal peptide having a von Heijne score of 9.4.

Furthermore, the polypeptides encoded by the extended or full-length cDNAs may be screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. Some of the results obtained for the polypeptides encoded by full-length cDNAs that were screened for the presence of known protein signatures and motifs using the Proscan software from the GCG package and the Prosite database are provided below.

The protein of SEQ ID NO :10 encoded by the full-length cDNA SEQ ID NO:9 (internal designation 108-013-5-O-H9-FLC) shows homologies with a family of lysophospholipases conserved among eukaryotes (yeast, rabbit, rodents and human). In addition, some members of this family exhibit a calcium-independent phospholipase A2 activity (Portilla *et al.*, *J. Am. Soc. Nephro.*, 9 :1178-1186 (1998)). All members of this family exhibit the active site consensus GX SXG motif of carboxylesterases that is also found in the protein of SEQ ID NO:10 (position 54 to 58). In addition, this protein may be a membrane protein with one transmembrane domain as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 :685-686 (1994)). Taken together, these data suggest that the protein of SEQ ID NO:10 may play a role in fatty acid metabolism, probably as a phospholipase. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, diabetes, and neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. It may also be useful in modulating inflammatory responses to infectious agents and/or to suppress graft rejection.

The protein of SEQ ID NO: 12 encoded by the full-length cDNA SEQ ID NO:11 (internal designation 108-004-5-O-D10-FLC) shows remote homology to a subfamily of beta4-galactosyltransferases widely conserved in animals (human, rodents, cow and chicken). Such enzymes, usually type II membrane proteins located in the endoplasmic reticulum or in the Golgi apparatus, catalyze the biosynthesis of glycoproteins, glycolipid glycans and lactose. Their characteristic features defined as those of subfamily A in Breton *et al.*, *J. Biochem.*, 123:1000-1009 (1998) are pretty well conserved in the protein of SEQ ID NO: 12, especially the region I containing the DVD motif (positions 163-165) thought to be involved either in UDP binding or in the catalytic process itself. In addition, the protein of SEQ ID NO: 12 has the typical structure of a type II protein. Indeed, it contains a short 28-amino-acid-long N-terminal tail, a transmembrane segment from positions 29 to 49 and a large 278-amino-acid-long C-terminal tail as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 :685-686 (1994)). Taken together, these data suggest that the protein of SEQ ID NO: 12 may play a role in the biosynthesis of polysaccharides, and of the carbohydrate moieties of glycoproteins and glycolipids and/or in cell-cell recognition. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, atherosclerosis, cardiovascular disorders, autoimmune disorders and rheumatic diseases including rheumatoid arthritis.

5 The protein of SEQ ID NO: 14 encoded by the extended cDNA SEQ ID NO: 13 (internal designation 108-004-5-0-E8-FLC) exhibits the typical PROSITE signature for amino acid permeases (positions 5 to 66) which are integral membrane proteins involved in the transport of amino acids into the cell. In addition, the protein of SEQ ID NO: 14 has a transmembrane segment from positions 9 to 29 as predicted by the
10 software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10:685-686 (1994)). Taken together, these data suggest that the protein of SEQ ID NO: 14 may be involved in amino acid transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, aminoacidurias, neurodegenerative diseases, anorexia, chronic fatigue, coronary vascular disease,
15 diphtheria, hypoglycemia, male infertility, muscular and myopathies.

20 Bacterial clones containing plasmids containing the full length cDNAs described above are presently stored in the inventor's laboratories under the internal identification numbers provided above. The inserts may be recovered from the deposited materials by growing an aliquot of the appropriate bacterial clone in the appropriate medium. The plasmid DNA can then be isolated using plasmid isolation procedures familiar to those skilled in the art such as alkaline lysis minipreps or large scale alkaline lysis plasmid
25 isolation procedures. If desired the plasmid DNA may be further enriched by centrifugation on a cesium chloride gradient, size exclusion chromatography, or anion exchange chromatography. The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the cDNA insertion. The PCR product which corresponds to the cDNA can then be manipulated using standard
30 cloning techniques familiar to those skilled in the art.

35 The above procedure was also used to obtain the cDNAs of the invention having the sequences of SEQ ID NOs: 24-73. Table I provides the sequence identification numbers of the cDNAs of the present invention, the locations of the first and last nucleotides of the full coding sequences in SEQ ID NOs: 24-73 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS
40 location in Table I), the locations of the first and last nucleotides in SEQ ID NOs: 24-73 which encode the signal peptides (listed under the heading SigPep Location in Table I), the locations of the first and last nucleotides in SEQ ID NOs: 24-73 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table I), the locations in SEQ ID NOs: 24-73 of stop codons (listed under the heading Stop Codon Location in Table I), the locations of the first and
45 last nucleotides in SEQ ID NOs: 24-73 of the polyA signals (listed under the heading Poly A Signal Location in Table I) and the locations of the first and last nucleotides of the polyA sites (listed under the heading Poly A Site Location in Table I).

50 Table II lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 74-123, the locations of the first and last amino acid residues of SEQ ID NOs: 74-123 in the full length polypeptide (second column), the locations of the first and last amino acid residues of SEQ ID NOs: 74-123 in the signal peptides (third column), and the locations of the first and last amino acid residues of SEQ ID NOs: 74-123 in

the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 24-73 and the amino acid sequences encoded by SEQ ID NOs: 24-73 (i.e. amino acid sequences of SEQ ID NOs: 74-123) are provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some incorrect or ambiguous sequences or amino acids. All instances of the symbol "n" in the nucleic acid sequences mean that the nucleotide can be adenine, guanine, cytosine or thymine. For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. In some instances the polypeptide sequences in the Sequence Listing contain the symbol "Xaa." These "Xaa" symbols indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where applicants believe one should not exist (if the sequence were determined more accurately). Thus, "Xaa" indicates that a residue may be any of the twenty amino acids. In some instances, several possible identities of the unknown amino acids may be suggested by the genetic code.

The sequences of SEQ ID NOs: 24-73 can readily be screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences encoded by the DNA containing the error or ambiguity. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its sequence.

EXAMPLE 15

Categorization of cDNAs of the Present Invention

The nucleic acid sequences of the present invention (SEQ ID NOs. 24-73) were grouped based on their homology to known sequences as follows. All sequences were compared to EMBL release 58 and daily releases available at the time of filing using BLASTN.

In some instances, the cDNAs did not match any known vertebrate sequence nor any publicly available EST sequence, thus being completely new.

All sequences exhibiting more than 90% of homology to known sequences over at least 30 nucleotides were retrieved and further analyzed. Table III gives the sequence identification numbers of these cDNAs (first column) and the positions of preferred fragments within these sequences (second column entitled "Positions of preferred fragments"). Each fragment is represented by x-y where x and y are the start and end positions respectively of a given preferred fragment. Preferred fragments are separated from each other by a coma. As used herein the term "polynucleotide described in Table III" refers to the all of the preferred

5 polynucleotide fragments defined in Table III in this manner. The present invention encompasses isolated, purified, or recombinant nucleic acids which consist of, consist essentially of, or comprise a contiguous span of one of the sequences of SEQ ID Nos. 24-73 or a sequence complementary thereto, said contiguous span comprising at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or
10 2000 nucleotides of the sequence of SEQ ID Nos. 24-73 or a sequence complementary thereto, to the extent that a contiguous span of these lengths is consistent with the lengths of the particular sequence, wherein the contiguous span comprises at least 1, 2, 3, 5, 10, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 of a polynucleotide described in Table III, or a sequence complementary thereto. The present invention also encompasses isolated, purified, or recombinant nucleic acids comprising, consisting essentially of,
15 or consisting of a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 nucleotides of a polynucleotide described in Table III or a sequence complementary thereto, to the extent that a contiguous span of these lengths is consistent with the length of the particular sequence described in Table III. The present invention also encompasses isolated, purified, or recombinant nucleic acids which comprise, consist of or consist essentially of a polynucleotide described in
20 Table III, or a sequence complementary thereto. The present invention further encompasses any combination of the nucleic acids listed in this paragraph.

25 Cells containing the cDNAs (SEQ ID NOs: 24-73) of the present invention in the vector pBluescriptII SK- (Stratagene) are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

30 A pool of the cells containing the cDNAs (SEQ ID NOs: 24-73), from which the cells containing a particular polynucleotide is obtainable, was deposited on June, 17, 1999, with the European Collection of Cell Cultures (ECACC), Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom. In addition, a pool of the cells containing the extended cDNAs (SEQ ID NOs: 47-73), from which the
35 cells containing a particular polynucleotide is obtainable, was deposited on December 18, 1998, with the European Collection of Cell Cultures (ECACC), Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom. Each cDNA clone has been transfected into separate bacterial cells (E-coli) for these composite deposits. In particular, cells containing the sequences of SEQ ID Nos: 25-40 and 42-46 were
40 deposited on June, 17, 1999 in the pool having ECACC Accession No. 99061735 and designated SignalTag 15061999. In addition, cells containing the sequences of SEQ ID Nos: 47-73 were deposited on December 18, 1998, in the pool having ECACC Accession No. 98121805 and designated SignalTag 166-191. Table IV provides the internal designation number assigned to each SEQ ID NO. and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

45 Each cDNA can be removed from the Bluescript vector in which it was deposited by performing a
50 Bsh II double digestion to produce the appropriate fragment for each clone provided the cDNA clone

sequence does not contain this restriction site. Alternatively, other restriction enzymes of the multicloning site of the vector may be used to recover the desired insert as indicated by the manufacturer.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40°C and 80°C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with $(-\text{[}^{32}\text{P]ATP}$ (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4×10^6 dpm/pmol.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 ml per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1×10^6 dpm/ml. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 ml of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

5 The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

10 The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the cDNA insertion. The PCR product which corresponds to the cDNA can then be manipulated using standard cloning techniques familiar to those skilled in the art.

15 Alternatively, the cDNA clone obtained by the process described in Examples 1 through 13 may not include the entire coding sequence of the protein encoded by the corresponding mRNA, although they do include sequences derived from the 5' ends of their corresponding mRNA. Such 5' EST can be used to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. Such obtained extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site. Examples 16 and 17 below describe methods for obtaining extended cDNAs using 5' ESTs. Example 17 also describes methods to obtain cDNA, mRNA or genomic DNA homologous to
20 cDNA, 5' ESTs, or fragment thereof.

25 The methods of Examples 16 and 17 can also be used to obtain cDNAs which encode less than the entire coding sequence of proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the cDNAs isolated using these methods encode at least 5, 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 consecutive amino acids of one of the proteins encoded by the sequences of
30 SEQ ID NOs. 24-73.

EXAMPLE 16

General Method for Using 5' ESTs to Clone and Sequence cDNAs which Include the Entire Coding Region and the Authentic 5' End of the Corresponding mRNA

35 The following general method may be used to quickly and efficiently isolate cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method, illustrated in Figure 3, may be applied to obtain cDNAs for any 5' EST.

40 The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly dT primer containing a nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. Such a primer and a commercially-available reverse transcriptase enzyme are added to a buffered
30 mRNA sample yielding a reverse transcript anchored at the 3' polyA site of the RNAs. Nucleotide monomers are then added to complete the first strand synthesis. After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer can be eliminated with an exclusion column.

45 Subsequently, a pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers is either based on GC content and melting temperatures of
50

oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais *et al.*, *Nucleic Acids Res.* 19: 3887-3891, 1991) such as PC-Rare ([http:// bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html](http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html)). Preferably, the nested primers at the 5' end and the nested primers at the 3' end are separated from one another by four to nine bases. These primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

A first PCR run is performed using the outer primer from each of the nested pairs. A second PCR run using the inner primer from each of the nested pairs is then performed on a small aliquot of the first PCR product. Thereafter, the primers and remaining nucleotide monomers are removed.

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the entire coding sequence. Such a cDNA may be used in a direct cloning procedure such as the one described in example 4.

However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. For such amplicons which do not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products. Once the full coding sequence has been completely determined, new primers compatible for PCR use are then designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in Figure 3. Such obtained cDNAs are then cloned into an appropriate vector using a procedure essentially similar to the one described in example 4.

Full-length PCR products are then sequenced using a procedure similar to the one described in example 11. Completion of the sequencing of a given cDNA fragment may be assessed by comparing the sequence length to the size of the corresponding nested PCR product. When Northern blot data are available, the size of the mRNA detected for a given PCR product may also be used to finally assess that the sequence is complete. Sequences which do not fulfill these criteria are discarded and will undergo a new isolation procedure.

Full-length PCR products are then cloned in an appropriate vector. For example, the cDNAs can be cloned into a vector using a procedure similar to the one described in example 4. Such full-length cDNA clones are then double-sequenced and submitted to computer analyses using procedure essentially similar to the ones described in Examples 11 through 13. However, it will be appreciated that full-length cDNA clones obtained from amplicons lacking part of the 3'UTR may lack polyadenylations sites and signals.

EXAMPLE 17

Methods for Obtaining cDNAs or Nucleic Acids Homologous to cDNAs or Fragments Thereof

In addition to PCR based methods for obtaining cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the cDNA is derived, mRNAs corresponding to the cDNAs, or nucleic acids which are homologous to cDNAs or fragments thereof. Indeed, cDNAs of the present invention or fragments thereof, including 5'ESTs, may also be used to isolate cDNAs or nucleic acids homologous to cDNAs from a cDNA library or a genomic DNA library as follows. Such cDNA libraries or genomic DNA libraries may be obtained from a commercial source or made using techniques familiar to those skilled in the art such as the one described in Examples 1 through 5. An example of such hybridization-based methods is provided below.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual 2d Ed.*, Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the cDNA or fragment thereof is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the cDNA or fragment thereof. More preferably, the probe comprises 20 to 30 consecutive nucleotides from the cDNA or fragment thereof. In some embodiments, the probe comprises more than 30 nucleotides from the cDNA or fragment thereof.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, *in vitro* transcription, and non radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After blocking of non specific sites, the filter is incubated with the labeled probe for an amount of time sufficient to allow binding of the probe to cDNAs or genomic DNAs containing a sequence capable of hybridizing thereto.

By varying the stringency of the hybridization conditions used to identify cDNAs or genomic DNAs which hybridize to the detectable probe, cDNAs or genomic DNAs having different levels of homology to the probe can be identified and isolated as described below.

1. Isolation of cDNA or Genomic DNA Sequences Having a High Degree of Homology to the Labeled Probe

To identify cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (T_m) is calculated using the formula: $T_m = 81.5 + 16.6(\log(Na^+)) + 0.41(\text{fraction G+C}) - (600/N)$ where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation $T_m = 81.5 + 16.6(\log(Na^+)) + 0.41(\text{fraction G+C}) - (0.63\% \text{ formamide}) - (600/N)$ where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 μ g denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 μ g denatured

5 fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook *et al.*, *supra*.

10 Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization
5 solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the T_m. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the T_m. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately
15 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

20 All of the foregoing hybridizations would be considered to be under "stringent" conditions.

Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15
minutes. The filter is then washed with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour.
15 Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

25 cDNAs or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

2. Isolation of cDNA or Genomic DNA Sequences Having Lower Degrees of Homology to the Labeled

Probe

30 The above procedure may be modified to identify cDNAs or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain cDNAs or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a
35 sodium concentration of approximately 1M. Following hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

40 Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer
30 may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below
45 25% formamide. cDNAs or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

3. Determination of the Degree of Homology between the Obtained cDNAs or Genomic DNAs and cDNAs or 50 Fragments thereof Used as the Labeled Probe or Between the Polypeptides Encoded by the Obtained

5 cDNAs or Genomic DNAs and the Polypeptides Encoded by the cDNAs or Fragment Thereof Used as the
Labeled Probe

10 To determine the level of homology between the hybridized cDNA or genomic DNA and the cDNA
or fragment thereof from which the probe was derived, the nucleotide sequences of the hybridized nucleic
5 acid and the cDNA or fragment thereof from which the probe was derived are compared. The sequences of
the cDNA or fragment thereof from which the probe was derived and the sequences of the cDNA or genomic
DNA which hybridized to the detectable probe may be stored on a computer readable medium as described
below and compared to one another using any of a variety of algorithms familiar to those skilled in the art
15 such as those described below.

20 To determine the level of homology between the polypeptide encoded by the hybridizing cDNA or
genomic DNA and the polypeptide encoded by the cDNA or fragment thereof from which the probe was
derived, the polypeptide sequence encoded by the hybridized nucleic acid and the polypeptide sequence
25 encoded by the cDNA or fragment thereof from which the probe was derived are compared. The sequences
of the polypeptide encoded by the cDNA or fragment thereof from which the probe was derived and the
polypeptide sequence encoded by the cDNA or genomic DNA which hybridized to the detectable probe may
be stored on a computer readable medium as described below and compared to one another using any of a
variety of algorithms familiar to those skilled in the art such as those described below.

30 Protein and/or nucleic acid sequence homologies may be evaluated using any of the variety of sequence
comparison algorithms and programs known in the art. Such algorithms and programs include, but are by
no means limited to, TBLASTN, BLASTP, FASTA, TFASTA, and CLUSTALW (Pearson and Lipman, 1988,
Proc. Natl. Acad. Sci. USA 85(8):2444-2448; Altschul *et al.*, 1990, *J. Mol. Biol.* 215(3):403-410; Thompson *et*
al., 1994, *Nucleic Acids Res.* 22(2):4673-4680; Higgins *et al.*, 1996, *Methods Enzymol.* 266:383-402;
Altschul *et al.*, 1990, *J. Mol. Biol.* 215(3):403-410; Altschul *et al.*, 1993, *Nature Genetics* 3:266-272).

35 In a particularly preferred embodiment, protein and nucleic acid sequence homologies are
evaluated using the Basic Local Alignment Search Tool ("BLAST") which is well known in the art (see, e.g.,
Karlin and Altschul, 1990, *Proc. Natl. Acad. Sci. USA* 87:2267-2268; Altschul *et al.*, 1990, *J. Mol. Biol.*
215:403-410; Altschul *et al.*, 1993, *Nature Genetics* 3:266-272; Altschul *et al.*, 1997, *Nuc. Acids Res.*
40 25:3389-3402). In particular, five specific BLAST programs are used to perform the following task:

- 45 (1) BLASTP and BLAST3 compare an amino acid query sequence against a protein sequence
30 database;
- (2) BLASTN compares a nucleotide query sequence against a nucleotide sequence database;
- (3) BLASTX compares the six-frame conceptual translation products of a query nucleotide sequence
45 (both strands) against a protein sequence database;
- (4) TBLASTN compares a query protein sequence against a nucleotide sequence database translated
35 in all six reading frames (both strands); and
- 50 (5) TBLASTX compares the six-frame translations of a nucleotide query sequence against the six-
frame translations of a nucleotide sequence database.

5 The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (*i.e.*, aligned) by means of a scoring matrix, many of which are known
10 in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet *et al.*, 1992, *Science* 258:1443-1445; Henikoff and Henikoff, 1993, *Proteins* 17:49-61). Less preferably, the PAM or PAM250 matrices may also be used (see, *e.g.*, Schwartz and Dayhoff, eds., 1978, *Matrices for Detecting Distance Relationships: Atlas of Protein Sequence and Structure*, Washington: National Biomedical Research
15 Foundation)

10 The BLAST programs evaluate the statistical significance of all high-scoring segment pairs identified, and preferably selects those segments which satisfy a user-specified threshold of significance, such as a user-specified percent homology. Preferably, the statistical significance of a high-scoring segment pair is evaluated using the statistical significance formula of Karlin (see, *e.g.*, Karlin and Altschul, 1990, *Proc. Natl. Acad. Sci. USA* 87:2267-2268).

15 The parameters used with the above algorithms may be adapted depending on the sequence length and degree of homology studied. In some embodiments, the parameters may be the default parameters used by the algorithms in the absence of instructions from the user.

In some embodiments, the level of homology between the hybridized nucleic acid and the cDNA or fragment thereof from which the probe was derived may be determined using the FASTDB algorithm
20 described in Brutlag *et al.* *Comp. App. Biosci.* 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the sequence which hybridizes to the probe, whichever is shorter. Because the FASTDB program does not consider 5' or 3' truncations when calculating homology levels, if the sequence which hybridizes to the probe
25 is truncated relative to the sequence of the cDNA or fragment thereof from which the probe was derived the homology level is manually adjusted by calculating the number of nucleotides of the cDNA or fragment thereof which are not matched or aligned with the hybridizing sequence, determining the percentage of total nucleotides of the hybridizing sequence which the non-matched or non-aligned nucleotides represent, and subtracting this percentage from the homology level. For example, if the hybridizing sequence is 700
30 nucleotides in length and the cDNA or fragment thereof sequence is 1000 nucleotides in length wherein the first 300 bases at the 5' end of the cDNA or fragment thereof are absent from the hybridizing sequence, and wherein the overlapping 700 nucleotides are identical, the homology level would be adjusted as follows. The non-matched, non-aligned 300 bases represent 30% of the length of the cDNA or fragment thereof. If the overlapping 700 nucleotides are 100% identical, the adjusted homology level would be 100-30=70%
35 homology. It should be noted that the preceding adjustments are only made when the non-matched or non-aligned nucleotides are at the 5' or 3' ends. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

For example, using the above methods, nucleic acids having at least 95% nucleic acid homology, at least 96% nucleic acid homology, at least 97% nucleic acid homology, at least 98% nucleic acid homology, at least 99% nucleic acid homology, or more than 99% nucleic acid homology to the cDNA or fragment thereof from which the probe was derived may be obtained and identified. Such nucleic acids may be allelic variants or related nucleic acids from other species. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the cDNA or fragment thereof from which the probe was derived.

Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied, for example the default parameters used by the algorithms in the absence of instructions from the user, one can obtain nucleic acids encoding proteins having at least 99%, at least 98%, at least 97%, at least 96%, at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the protein encoded by the cDNA or fragment thereof from which the probe was derived. In some embodiments, the homology levels can be determined using the "default" opening penalty and the "default" gap penalty, and a scoring matrix such as PAM 250 (a standard scoring matrix; see Dayhoff *et al.*, in: Atlas of Protein Sequence and Structure, Vol. 5, Supp. 3 (1978)).

Alternatively, the level of polypeptide homology may be determined using the FASTDB algorithm described by Brutlag *et al.* Comp. App. Biosci. 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=Sequence Length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the homologous sequence, whichever is shorter. If the homologous amino acid sequence is shorter than the amino acid sequence encoded by the cDNA or fragment thereof as a result of an N terminal and/or C terminal deletion the results may be manually corrected as follows. First, the number of amino acid residues of the amino acid sequence encoded by the cDNA or fragment thereof which are not matched or aligned with the homologous sequence is determined. Then, the percentage of the length of the sequence encoded by the cDNA or fragment thereof which the non-matched or non-aligned amino acids represent is calculated. This percentage is subtracted from the homology level. For example wherein the amino acid sequence encoded by the cDNA or fragment thereof is 100 amino acids in length and the length of the homologous sequence is 80 amino acids and wherein the amino acid sequence encoded by the cDNA or fragment thereof is truncated at the N terminal end with respect to the homologous sequence, the homology level is calculated as follows. In the preceding scenario there are 20 non-matched, non-aligned amino acids in the sequence encoded by the cDNA or fragment thereof. This represents 20% of the length of the amino acid sequence encoded by the cDNA or fragment thereof. If the remaining amino acids are 100% identical between the two sequences, the homology level would be 100%-20%=80% homology. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

In addition to the above described methods, other protocols are available to obtain homologous cDNAs using cDNA of the present invention or fragment thereof as outlined in the following paragraphs.

5 cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing polyA selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the polyA tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

10 5 The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of SEQ ID NOs 24-73. Preferably, the primer comprises at least 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides from the sequences of SEQ ID NOs 24-73. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of SEQ ID NOs 24-73. If
15 it is desired to obtain cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RT-PCR may be performed as described above using primers from both ends of the cDNA to
20 be obtained.

cDNAs containing 5' fragments of the mRNA may be prepared by hybridizing an mRNA comprising
15 the sequences of SEQ ID NOs. 24-73 with a primer comprising a complementary to a fragment of the known cDNA, genomic DNA or fragment thereof hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least
25 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides of the sequences complementary to SEQ ID NOs. 24-73.

30 20 Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded cDNAs made using the methods described above are isolated and cloned.
35 The cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.
25

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. 1997
40 and Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, 1989.
30

45 Alternatively, other procedures may be used for obtaining full-length cDNAs or homologous cDNAs. In one approach, cDNAs are prepared from mRNA and cloned into double stranded phagemids as follows. The cDNA library in the double stranded phagemids is then rendered single stranded by treatment with an
35 endonuclease, such as the Gene II product of the phage F1 and an exonuclease (Chang *et al.*, *Gene* 127:95-8, 1993). A biotinylated oligonucleotide comprising the sequence of a fragment of a known cDNA, genomic DNA or fragment thereof is hybridized to the single stranded phagemids. Preferably, the fragment
50

comprises at least 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides of the sequences of SEQ ID NOs. 24-73.

Hybrids between the biotinylated oligonucleotide and phagemids are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet (Fry *et al.*, *Biotechniques*, 13: 124-131, 1992). Thereafter, the resulting phagemids are released from the beads and converted into double stranded DNA using a primer specific for the cDNA or fragment thereof used to design the biotinylated oligonucleotide. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The resulting double stranded DNA is transformed into bacteria. Homologous cDNAs or full length cDNAs containing the cDNA or fragment thereof sequence are identified by colony PCR or colony hybridization.

Using any of the above described methods, a plurality of cDNAs containing full-length protein coding sequences or fragments of the protein coding sequences may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

cDNAs prepared by any method described therein may be subsequently engineered to obtain nucleic acids which include desired fragments of the cDNA using conventional techniques such as subcloning, PCR, or *in vitro* oligonucleotide synthesis. For example, nucleic acids which include only the full coding sequences (*i.e.* the sequences encoding the signal peptide and the mature protein remaining after the signal peptide is cleaved off) may be obtained using techniques known to those skilled in the art. Alternatively, conventional techniques may be applied to obtain nucleic acids which contain only the coding sequence for the mature protein remaining after the signal peptide is cleaved off or nucleic acids which contain only the coding sequences for the signal peptides.

Similarly, nucleic acids containing any other desired fragment of the coding sequences for the encoded protein may be obtained. For example, the nucleic acid may contain at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 consecutive bases of a cDNA.

Once a cDNA has been obtained, it can be sequenced to determine the amino acid sequence it encodes. Once the encoded amino acid sequence has been determined, one can create and identify any of the many conceivable cDNAs that will encode that protein by simply using the degeneracy of the genetic code. For example, allelic variants or other homologous nucleic acids can be identified as described below. Alternatively, nucleic acids encoding the desired amino acid sequence can be synthesized *in vitro*.

In a preferred embodiment, the coding sequence may be selected using the known codon or codon pair preferences for the host organism in which the cDNA is to be expressed.

IV. Use of cDNA or Fragments Thereof to Express Proteins and Uses of Those Expressed Proteins

Using any of the above described methods, cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described below. If desired, the cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding

sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

EXAMPLE 1B

Expression of the Proteins Encoded by cDNAs or Fragments Thereof

To express the proteins encoded by the cDNAs or fragments thereof, nucleic acids containing the coding sequence for the proteins or fragments thereof to be expressed are obtained as described above and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 24-73 listed in Table I and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 24-73 as defined in Table I above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table I as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 24-73. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 24-73 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table I. Similarly, should the extent of the full length polypeptides differ from those indicated in Table II as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table II.

Alternatively, the nucleic acid used to express the protein or fragment thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 24-73 as defined in Table I above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table I as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 24-73. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the mature protein encoded by one of SEQ ID NOs. 24-73 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table I. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table I, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal

5 peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table II as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 74-123 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table II. Thus, 10 5 claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences listed in Table II, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically 15 active form of the polypeptides included in the sequence of one of SEQ ID NOs. 74-123 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table II or the nucleotides encoding the mature polypeptide in Table I as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification 20 of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and 15 the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypeptides comprising the mature protein included in one of SEQ ID NOs. 74-123 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 24-73 encoding the mature protein shall not be 25 construed to exclude any readily identifiable variations from the sequences listed in Table I and Table II.

In some embodiments, the nucleic acid used to express the protein or fragment thereof may 30 20 comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 24-73 as defined in Table I above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table I as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, 35 25 or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID NOs. 24-73. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID NOs. 24-73 is not to be construed as excluding any readily identifiable variations from the sequences 40 listed in Table I. Similarly, should the extent of the signal peptides differ from those indicated in Table II as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 74-123 is not to be construed as 30 excluding any readily identifiable variations from the sequences listed in Table II.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 5 consecutive amino acids of one of the sequences of SEQ ID NOs: 74-123. In some embodiments, the nucleic acid may encode 35 50 a polypeptide comprising at least 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 consecutive amino acids of one of the sequences of SEQ ID NOs: 74-123.

5 The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

10 The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, *et al.*, U.S. Patent No. 5,082,767.

20 The following is provided as one exemplary method to express the proteins encoded by the cDNAs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using BglI and SalI restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a fragment of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The cDNA or fragment thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the cDNA or fragment thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and BglII at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

40 The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

45 Alternatively, the cDNAs may be cloned into pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA). The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the cDNA is released into the culture medium thereby facilitating purification.

5 Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

10 As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

15 Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, cDNA, or fragment thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, cDNA, or fragment thereof.

20 Secreted proteins from the host cells or organisms containing an expression vector which contains the cDNA or a fragment thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

25 Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or fragment thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or fragment thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or fragment thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

30 The protein encoded by the cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

35 If antibody production is not possible, the cDNA sequence or fragment thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the cDNA or fragment thereof is inserted in frame with the gene encoding the other half of the chimera. The other half of the chimera may be β -globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β -globin or nickel attached thereto is then

5 used to purify the chimeric protein. Protease cleavage sites may be engineered between the β -globin gene or the nickel binding polypeptide and the cDNA or fragment thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

10 One useful expression vector for generating β -globin chimerics is pSG5 (Stratagene), which encodes rabbit β -globin. Intron II of the rabbit β -globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis *et al.*, (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from 15 Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using *in vitro* translation systems such as the *In vitro* Express™ Translation Kit (Stratagene).

20 Following expression and purification of the secreted proteins encoded by the 5' ESTs, cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described 25 below, as well as other biological roles for which assays for determining activity are available.

25 Alternatively, the polypeptide to be expressed may also be a product of transgenic animals, i.e., as a component of the milk of transgenic cows, goats, pigs or sheeps which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein of interest.

30 EXAMPLE 19

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

35 The proteins encoded by the cDNAs, or fragments thereof are cloned into expression vectors such as those described in the previous example. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated 40 with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent 45 molecule, attached thereto.

50 Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding 55 reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the cDNAs or fragments thereof made using any of the methods described therein may be evaluated to determine their physiological activities as described below.

EXAMPLE 20

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above cDNAs or fragments thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan *et al.*, Greene Publishing Associates and Wiley-Interscience; Takai *et al.* *J. Immunol.* 137:3494-3500, 1986. Bertagnolli *et al.* *J. Immunol.* 145:1706-1712, 1990. Bertagnolli *et al.*, *Cellular Immunology* 133:327-341, 1991. Bertagnolli, *et al.* *J. Immunol.* 149:3778-3783, 1992; Bowman *et al.*, *J. Immunol.* 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology, J.E. Coligan *et al.* Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in Immunology, *supra* Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries *et al.*, *J. Exp. Med.* 173:1205-1211, 1991; Moreau *et al.*, *Nature* 36:690-692, 1988; Greenberger *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology, J.E. Coligan *et al.*, Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (*In vitro* Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger *et al.*, *Proc. Natl. Acad. Sci. USA* 77:6091-6095, 1980; Weinberger *et al.*, *Eur. J. Immun.* 11:405-411, 1981; Takai *et al.*, *J. Immunol.* 137:3494-3500, 1986; Takai *et al.*, *J. Immunol.* 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 21

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (*In vitro* Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan *et al.* Eds, Greene Publishing Associates and Wiley-Interscience; Hermann *et al.*, *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Hermann *et al.*, *J. Immunol.* 128:1968-1974, 1982; Handa *et al.*, *J. Immunol.* 135:1564-1572, 1985; Takai *et al.*, *J. Immunol.* 137:3494-3500, 1986; Takai *et al.*, *J. Immunol.* 140:508-512, 1988; Hermann *et al.*, *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Hermann *et al.*, *J. Immunol.* 128:1968-1974, 1982; Handa *et al.*, *J. Immunol.* 135:1564-1572, 1985; Takai *et al.*, *J. Immunol.* 137:3494-3500, 1986; Bowman *et al.*, *J. Virology* 61:1992-1998; Takai *et al.*, *J. Immunol.* 140:508-512, 1988; Bertagnoli *et al.*, *Cellular Immunology* 133:327-341, 1991; Brown *et al.*, *J. Immunol.* 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology, J.E. Coligan *et al* Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (*In*

5 *vitro* Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan *et al.* Eds., Greene Publishing Associates and Wiley-Interscience; Takai *et al.*, *J. Immunol.* 137:3494-3500, 1986; Takai *et al.*; *J. Immunol.* 140:508-512, 1988; Bertagnoli *et al.*, *J. Immunol.* 149:3778-3783, 1992.

10 5 The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery *et al.*, *J. Immunol.* 134:536-544, 1995; Inaba *et al.*, *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia *et al.*, *Journal of Immunology* 154:5071-5079, 1995; Porgador *et al.*, *Journal of Experimental Medicine* 182:255-260, 1995; Nair *et al.*, 15 *Journal of Virology* 67:4062-4069, 1993; Huang *et al.*, *Science* 264:961-965, 1994; Macatonia *et al.*, *Journal of Experimental Medicine* 169:1255-1264, 1989; Bhardwaj *et al.*, *Journal of Clinical Investigation* 94:797-807, 1994; and Inaba *et al.*, *Journal of Experimental Medicine* 172:631-640, 1990.

20 The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz *et al.*, *Cytometry* 13:795-808, 1992; Gorczyca *et al.*, 15 *Leukemia* 7:659-670, 1993; Gorczyca *et al.*, *Cancer Research* 53:1945-1951, 1993; Itoh *et al.*, *Cell* 66:233-243, 1991; Zacharchuk, *Journal of Immunology* 145:4037-4045, 1990; Zamai *et al.*, *Cytometry* 14:891-897, 25 1993; Gorczyca *et al.*, *International Journal of Oncology* 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, 20 without limitation, those described in: Antica *et al.*, *Blood* 84:111-117, 1994; Fine *et al.*, *Cellular immunology* 155:111-122, 1994; Galy *et al.*, *Blood* 85:2770-2778, 1995; Toki *et al.*, *Proc. Nat. Acad. Sci. USA* 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. 35 For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as 40 bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, *Leishmania* spp., 45 *malaria* spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

35 Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, 50 autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent

5 diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable
10 using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both.
15 Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the
20 tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in
25 tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-
30 1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte
35 antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate
40 systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl.
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Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases.

Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells *in vivo*, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in

expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a fragment of (e.g., a cytoplasmic-domain truncated fragment) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 22

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the cDNAs or fragments thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson *et al.* *Cellular Biology* 15:141-151, 1995; Keller *et al.*, *Molecular and Cellular Biology* 13:473-486, 1993; McClanahan *et al.*, *Blood* 81:2903-2915, 1993.

The proteins encoded by the cDNAs or fragments thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. *Methylcellulose Colony Forming Assays*, in *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama *et al.*, *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. *Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential*, in *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben *et al.*, *Experimental Hematology* 22:353-359, 1994; Ploemacher, R.E. *Cobblestone Area Forming Cell Assay*, In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* Eds. pp. 1-21, Wiley-Liss,

Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells, R.I. Freshney, *et al.* Eds. pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells, R.I. Freshney, *et al.* Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoiesis is beneficial. For example, a protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 23

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Regulation of Tissue Growth

The proteins encoded by the cDNAs or fragments thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. WO95/16035, International Patent Publication No. WO95/05846 and International Patent Publication No. WO91/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration,

death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 24

Assaying the Proteins Expressed from cDNAs or Fragments

Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the cDNAs or fragments thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale *et al.*, *Endocrinology* 91:562-572, 1972; Ling *et al.*, *Nature* 321:779-782, 1986; Vale *et al.*, *Nature* 321:776-779, 1986; Mason *et al.*, *Nature* 318:659-663, 1985; Forage *et al.*, *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Greene Publishing Associates and Wiley-Interscience; Taub *et al.* *J. Clin. Invest.* 95:1370-

1376, 1995; Lind *et al.* *APMIS* 103:140-146, 1995; Muller *et al.* *Eur. J. Immunol.* 25:1744-1748; Gruber *et al.* *J. of Immunol.* 152:5860-5867, 1994; Johnston *et al.* *J. of Immunol.* 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 25

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the cDNAs or fragments thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

5 The activity of a protein of the invention may, among other means, be measured by the following methods:

10 Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub *et al.* *J. Clin. Invest.* 95:1370-1376, 1995; Lind *et al.* *APMIS* 103:140-146, 15 1995; Mueller *et al.* *Eur. J. Immunol.* 25:1744-1748; Gruber *et al.* *J. of Immunol.* 152:5860-5867, 1994; Johnston *et al.* *J. of Immunol.* 153:1762-1768, 1994.

EXAMPLE 26

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Regulation of Blood Clotting

15 The proteins encoded by the cDNAs or fragments thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet *et al.*, *J. Clin. Pharmacol.* 26:131-140, 1986; Burdick *et al.*, *Thrombosis Res.* 45:413-419, 1987; Humphrey *et al.*, *Fibrinolysis* 5:71-79 (1991); Schaub, *Prostaglandins* 35:467-474, 1988.

20 Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds 25 resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the 30 proteins as desired.

EXAMPLE 27

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Involvement in Receptor/Ligand Interactions

45 The proteins encoded by the cDNAs or a fragment thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in *Current Protocols in Immunology*, J.E. Coligan 50

et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai *et al.*, *Proc. Natl. Acad. Sci. USA* 84:6864-6868, 1987; Bierer *et al.*, *J. Exp. Med.* 168:1145-1156, 1988; Rosenstein *et al.*, *J. Exp. Med.* 169:149-160, 1989; Stoltzenberg *et al.*, *J. Immunol. Methods* 175:59-68, 1994; Stitt *et al.*, *Cell* 80:661-670, 1995; Gyuris *et al.*, *Cell* 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 28

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Anti-Inflammatory Activity

The proteins encoded by the cDNAs or a fragment thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

EXAMPLE 29

Assaying the Proteins Expressed from cDNAs or Fragments Thereof for Tumor Inhibition Activity

The proteins encoded by the cDNAs or a fragment thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors,

agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 30

Identification of Proteins which Interact with Polypeptides Encoded by cDNAs

Proteins which interact with the polypeptides encoded by cDNAs or fragments thereof, such as receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the cDNAs or fragments thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the cDNAs or fragments thereof are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the cDNAs or fragments thereof.

Alternatively, the system described in Lustig *et al.*, Methods in Enzymology 283: 83-99 (1997), may be used for identifying molecules which interact with the polypeptides encoded by cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing cDNA inserts cloned

5 downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes. The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for
10 5 interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the cDNA or a fragment thereof can be constructed. In some versions, of this method the affinity column
15 contains chimeric proteins in which the protein encoded by the cDNA or a fragment thereof is fused to glutathione S-transferase. A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen *et al.* Electrophoresis,
20 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to
15 screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by cDNAs or fragments thereof can also be
25 screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting
20 molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethyl dextran matrix) and a sample of test molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field
30 (which extend a few hundred nanometers from the sensor surface). In these screening assays, the target
35 molecule can be one of the polypeptides encoded by cDNAs or a fragment thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are
40 extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique
30 polypeptides encoded by the cDNAs or fragments thereof.

To study the interaction of the proteins encoded by the cDNAs or fragments thereof with drugs, the
45 microdialysis coupled to HPLC method described by Wang *et al.*, Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch *et al.*, J. Chromatogr. 777:311-328 (1997).

The system described in U.S. Patent No. 5,654,150, may also be used to identify molecules which
35 interact with the polypeptides encoded by the cDNAs. In this system, pools of cDNAs are transcribed and
50 translated *in vitro* and the reaction products are assayed for interaction with a known polypeptide or antibody.

5 It will be appreciated by those skilled in the art that the proteins expressed from the cDNAs or fragments may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins
10 expressed from the cDNAs or fragments thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the cDNAs or fragments thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described below. The antibodies may be capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 24-73, a mature protein encoded by one of the sequences of SEQ ID NOs. 24-73, or a signal peptide
15 encoded by one of the sequences of SEQ ID Nos. 24-73. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 74-123. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the cDNAs which comprise at least 15 amino acids of the
20 sequences of SEQ ID NOs: 74-123. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 74-123. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the cDNAs which comprise at least 40 amino acids of the
25 sequences of SEQ ID NOs: 74-123.

EXAMPLE 31

Production of an Antibody to a Human Protein

30 Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in example 18. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

25 A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., *Nature* 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few
40 micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are
45 diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., *Meth. Enzymol.* 35 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their

monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. *et al.* Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. *et al.* *J. Clin. Endocrinol. Metab.* 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. *et al.*, Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of cDNAs or Fragments Thereof as Reagents

The cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 32

Preparation of PCR Primers and Amplification of DNA

The cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases

5 in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana
10 5 Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid
15 sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

EXAMPLE 33

Use of cDNAs as Probes

20 Probes derived from cDNAs or fragments thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and
25 may be made using techniques known in the art, including *in vitro* transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured
30 prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony
35 hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or *in vitro* transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or
40 cDNA library which are capable of hybridizing to the detectable probe as described in example 17 above.

30 PCR primers made as described in example 32 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 34-38 below. Such analyses may utilize detectable probes or primers based on the sequences of the cDNAs or fragments thereof (or genomic DNAs obtainable therefrom).
45

EXAMPLE 34

Forensic Matching by DNA Sequencing

35 In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the
50
55

5 cDNAs (or genomic DNAs obtainable therefrom), is then utilized in accordance with example 32 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences
10 5 from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of
15 100 bases in length are used to prove identity between the suspect and the sample.

10 EXAMPLE 35

Positive Identification by DNA Sequencing

20 The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table I and the appended sequence listing. Preferably, 20 to 50 different primers
15 25 are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with example 32. Each of these DNA segments is sequenced, using the methods set forth in example 34. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

20 EXAMPLE 36

Southern Blot Forensic Identification

30 The procedure of example 35 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200
35 25 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with
40 30 skill in the art. For a review of Southern blotting see Davis *et al.* (Basic Methods in Molecular Biology, 1986, Elsevier Press, pp 62-65).

45 A panel of probes based on the sequences of the cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis *et al.*, *supra*). Preferably, the probe comprises at least 12, 15, or 17 consecutive
35 50 nucleotides from the cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the cDNA (or genomic DNAs obtainable

therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

EXAMPLE 37

Dot Blot Identification Procedure

Another technique for identifying individuals using the cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp in length are synthesized that correspond to at least 10, preferably 50 sequences from the cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P^{32} using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and hybridized with labeled probe using techniques known in the art (Davis *et al. supra*). The ^{32}P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood *et al.*, *Proc. Natl. Acad. Sci. USA* 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 38 below provides a representative alternative fingerprinting procedure in which the probes are derived from cDNAs.

EXAMPLE 38

Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and XbaI. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 18 and 31 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

EXAMPLE 39

Identification of Tissue Types or Cell Species by Means of Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of antibody preparations according to Examples 18 and 31 which are conjugated, directly or indirectly to a detectable marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semi-qualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ion-exchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous antisera is suitable for either procedure.

A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. *et al.*, Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below.

Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example ^{125}I , and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 μm , unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. *et al.*, Section 19-2 in: Basic Methods in Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of

polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 μ l, and containing from about 1 to 100 μ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. *et al.*, (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 18 and 31. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign bodily sites.

In addition to their applications in forensics and identification, cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. example 40 below describes radiation hybrid (RH) mapping of human chromosomal regions using cDNAs. example 41 below describes a representative procedure for mapping a cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. example 42 below describes mapping of cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 40

Radiation hybrid mapping of cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different fragments of the human genome. This technique is described by Benham *et al.* (*Genomics* 4:509-517, 1989) and Cox *et al.*, (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from

a panel of 80-100 cell lines provides a mapping reagent for ordering cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler *et al.*, *Science* 274:540-546, 1996).

5 RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thymidine kinase (TK) (Foster *et al.*, *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr *et al.*, *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers *et al.*, *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer *et al.*, *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington *et al.*, *Genomics* 11:701-708, 1991).

EXAMPLE 41

Mapping of cDNAs to Human Chromosomes using PCR techniques

cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology: Principles and Applications for DNA Amplification, 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 μ Cu of a 32 P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single

human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter *et al.*, *Genomics* 6:475-481 (1990).)

Alternatively, the cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in example 42 below.

EXAMPLE 42

Mapping of cDNAs to Chromosomes Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of a cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990). Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 nM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCl (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 µg/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at 70°C, then dehydrated at 40°C. The slides are treated with proteinase K (10 µg/100 ml in 20 mM Tris-HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif *et al.*, *supra.*). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given chromosome.

EXAMPLE 43

Use of cDNAs to Construct or Expand Chromosome Maps

Once the cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 40-42 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja *et al. Genome Research* 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms chromosomes may be obtained.

As described in example 44 below cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 44

Identification of genes associated with hereditary diseases or drug response

This example illustrates an approach useful for the association of cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

CDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 40 and 41 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several diseases or phenotypes for which genes have not been

5 identified. The gene corresponding to this cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or
10 cDNA obtained from the patients. CDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating
15 that the gene containing the cDNA may be responsible for the genetic disease.

20 VI. Use of cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be
25 purified or enriched. Exemplary secretion vectors are described below.

EXAMPLE 45

Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus
30 promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from a cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 24-73 as defined in Table I above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell,
35 tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal
40 sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be
35 transiently present in the host. Preferably, the secretion vector is maintained in multiple copies in each host cell. As used herein, multiple copies means at least 2, 5, 10, 20, 25, 50 or more than 50 copies per cell. In
50

5 some embodiments, the multiple copies are maintained extrachromosomally. In other embodiments, the multiple copies result from amplification of a chromosomal sequence.

Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast
10 5 episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

15 After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using
20 conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth
25 media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene
30 encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The cDNAs or 5' ESTs may also be used to clone sequences located upstream of the cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer
35 25 sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. The next example describes a method for cloning sequences upstream of the cDNAs or 5' ESTs.

40 EXAMPLE 46

30 Use of cDNAs or Fragments thereof to Clone Upstream Sequences from Genomic DNA

Sequences derived from cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which
45 utilizes the GenomeWalker[®] kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA
35 50 fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer should be selected to be specific for the cDNA or 5' EST of interest and should have a melting temperature, length, and location in the cDNA or 5' EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 µl of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 µM each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc)₂, and 1 µl of the Tth polymerase 50X mix in a total volume of 50 µl. The reaction cycle for the first PCR reaction is as follows: 1 min at 94°C / 2 sec at 94°C, 3 min at 72°C (7 cycles) / 2 sec at 94°C, 3 min at 67°C (32 cycles) / 5 min at 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 µl of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 µl volume having a composition identical to that of the first PCR reaction except the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker® kit. The second nested primer is specific for the particular cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min at 94°C / 2 sec at 94°C, 3 min at 72°C (6 cycles) / 2 sec at 94°C, 3 min at 67°C (25 cycles) / 5 min at 67°C.

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing the cDNA or EST sequence are isolated as described in example 17 above. Thereafter, the single stranded DNA containing the cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or cDNA sequences are identified by colony PCR or colony hybridization.

Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described below.

EXAMPLE 47

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the cDNAs or fragment thereof are cloned into a suitable promoter reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, p β gal-Basic, p β gal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular cDNA or fragment thereof is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 48Cloning and Identification of Promoters

Using the method described in example 47 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:15) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:16), the promoter having the internal designation P13H2 (SEQ ID NO:17) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:18) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:19), the promoter having the internal designation P15B4 (SEQ ID NO:20) was obtained.

5 Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:21) and GAG ACC ACA
CAG CTA GAC AA (SEQ ID NO:22), the promoter having the internal designation P29B6 (SEQ ID NO:23)
was obtained.

10 Figure 4 provides a schematic description of the promoters isolated and the way they are
5 assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of
motifs resembling transcription factor binding sites or known transcription start sites using the computer
program MatInspector release 2.0, August 1996.

15 Figure 5 describes the transcription factor binding sites present in each of these promoters. The
columns labeled matrix provides the name of the MatInspector matrix used. The column labeled position
10 provides the 5' position of the promoter site. Numeration of the sequence starts from the transcription site as
determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation"
indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined
20 by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides
the MatInspector score found for this site. The column labeled "length" provides the length of the site in
15 nucleotides. The column labeled "sequence" provides the sequence of the site found.

25 The promoters and other regulatory sequences located upstream of the cDNAs or 5' ESTs may be
used to design expression vectors capable of directing the expression of an inserted gene in a desired
spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial,
temporal, developmental, and quantitative patterns may be selected using the results of the expression
30 analysis described in example 10 above. For example, if a promoter which confers a high level of
expression in muscle is desired, the promoter sequence upstream of a cDNA or 5' EST derived from an
mRNA which is expressed at a high level in muscle, as determined by the method of example 10, may be
used in the expression vector.

35 Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of
25 the desired insert downstream of the promoter, such that the promoter is able to drive expression of the
inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for
extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable
40 backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic
episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial
30 chromosomes.

45 Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction
sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression
vector.

50 Following the identification of promoter sequences using the procedures of Examples 46-48,
35 proteins which interact with the promoter may be identified as described in example 49 below.

EXAMPLE 49

Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or *in vitro* transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNase protection analysis.

VII. Use of cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 50 and 51 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

EXAMPLE 50

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green *et al.*, *Ann. Rev. Biochem.*, 55:569-597 (1986) and Izant and Weintraub, *Cell*, 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using *in vitro* transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids *in vivo* by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized *in vitro*. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies include 2' O-methyl RNA oligonucleotides and Protein-nucleic acid (PNA) oligonucleotides. Further examples are described by Rossi *et al.*, *Pharmacol. Ther.*, 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT WO94/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

5 The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

10 In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

15 Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

20 The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using *in vitro* expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

25 The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between $1 \times 10^{-10} \text{M}$ to $1 \times 10^{-4} \text{M}$. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of 1×10^{-7} translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

30 It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi *et al.*, *supra*.

35 In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

40 The cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it

is associated with a particular gene. The cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a fragment of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a fragment of the cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the cDNA or from the gene corresponding to the cDNA are contemplated within the scope of this invention.

EXAMPLE 51

Preparation and use of Triple Helix Probes

The sequences of the cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based upon the homologies of the target gene corresponding to the cDNA from which the oligonucleotide was derived with known gene sequences that have been associated with a particular function. The cell functions can also be predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the cDNA is associated with the disease using techniques described in example 44.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced *in vivo* using the techniques described above and in example 50 at a dosage calculated based on the *in vitro* results, as described in example 50.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize

the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin *et al.* (*Science*, 245:967-971 (1989)).

EXAMPLE 52

Use of cDNAs to Express an Encoded Protein in a Host Organism

The cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length cDNA encoding the signal peptide and the mature protein, or a cDNA encoding only the mature protein is introduced into the host organism. The cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells *in vitro*. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

EXAMPLE 53

Use Of Signal Peptides To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the cDNAs of the present invention or fragment thereof may also be used as a carrier to import a peptide or a protein of interest, so-called cargo, into tissue culture cells (Lin *et al.*, *J. Biol. Chem.*, 270: 14225-14258 (1995); Du *et al.*, *J. Peptide Res.*, 51: 235-243 (1998); Rojas *et al.*, *Nature Biotech.*, 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the cDNA sequence or fragment thereof encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin *et al.*, *supra*; Lin *et al.*, *J. Biol. Chem.*, 271: 5305-5308 (1996); Rojas *et al.*, *J. Biol. Chem.*, 271: 27456-27461 (1996); Liu *et al.*, *Proc. Natl. Acad. Sci. USA*, 93: 11819-11824 (1996); Rojas *et al.*, *Bioch. Biophys. Res. Commun.*, 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helices, as described in examples 50 and 51 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 54

Computer Embodiments

As used herein the term "cDNA codes of SEQ ID NOs. 24-73" encompasses the nucleotide sequences of SEQ ID NOs. 24-73, fragments of SEQ ID NOs. 24-73, nucleotide sequences homologous to SEQ ID NOs. 24-73 or homologous to fragments of SEQ ID NOs. 24-73, and sequences complementary to all of the preceding sequences. The fragments include fragments of SEQ ID NOs. 24-73 comprising at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 consecutive nucleotides of SEQ ID NOs. 24-73. Preferably, the fragments are novel fragments. Preferably the fragments include polynucleotides described in Table III or fragments thereof comprising at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 consecutive nucleotides of the polynucleotides described in Table III. Homologous sequences and fragments of SEQ ID NOs. 24-73 refer to a sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, or 75% homology to these sequences. Homology may be determined using any of the computer programs and parameters described in example 17, including BLAST2N with the default parameters or with any modified parameters. Homologous sequences also include RNA sequences in which uridines replace the thymines in the cDNA codes of SEQ ID NOs. 24-73. The homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a sequencing error as described above. Preferably the homologous sequences and fragments of SEQ ID NOs. 24-73 include polynucleotides described in Table III or fragments comprising at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 consecutive nucleotides of the polynucleotides described in Table III. It will be appreciated that the cDNA codes of SEQ ID NOs. 24-73 can be represented in the traditional single character format (See the inside back cover of Styer, Lubert. *Biochemistry*, 3rd edition. W. H. Freeman & Co., New York.) or in any other format which records the identity of the nucleotides in a sequence.

5 As used herein the term "polypeptide codes of SEQ ID NOS. 74-123" encompasses the polypeptide sequences of SEQ ID NOS. 74-123 which are encoded by the cDNAs of SEQ ID NOS. 24-73, polypeptide sequences homologous to the polypeptides of SEQ ID NOS. 74-123, or fragments of any of the preceding sequences. Homologous polypeptide sequences refer to a polypeptide sequence having at least 99%, 98%,
10 97%, 96%, 95%, 90%, 85%, 80%, 75% homology to one of the polypeptide sequences of SEQ ID NOS. 74-123. Homology may be determined using any of the computer programs and parameters described herein, including FASTA with the default parameters or with any modified parameters. The homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a
15 sequencing error as described above. The polypeptide fragments comprise at least 5, 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 150 or 200 consecutive amino acids of the polypeptides of SEQ ID NOS. 74-123. Preferably, the fragments are novel fragments. Preferably, the fragments include polypeptides encoded by the polynucleotides described in Table III, or fragments thereof comprising at least 5, 10, 15, 20, 25, 30, 35,
20 40, 50, 75, 100, or 150 consecutive amino acids of the polypeptides encoded by the polynucleotides described in Table III. It will be appreciated that the polypeptide codes of the SEQ ID NOS. 74-123 can be represented in the traditional single character format or three letter format (See the inside back cover of
25 Starier, Lubert. *Biochemistry*, 3rd edition. W. H Freeman & Co., New York.) or in any other format which relates the identity of the polypeptides in a sequence.

It will be appreciated by those skilled in the art that the cDNA codes of SEQ ID NOS. 24-73 and polypeptide codes of SEQ ID NOS. 74-123 can be stored, recorded, and manipulated on any medium which
30 can be read and accessed by a computer. As used herein, the words "recorded" and "stored" refer to a process for storing information on a computer medium. A skilled artisan can readily adopt any of the presently known methods for recording information on a computer readable medium to generate manufactures comprising one or more of the cDNA codes of SEQ ID NOS. 24-73, one or more of the polypeptide codes of SEQ ID NOS. 74-123. Another aspect of the present invention is a computer readable
35 medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 cDNA codes of SEQ ID NOS. 24-73. Another aspect of the present invention is a computer readable medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 polypeptide codes of SEQ ID NOS. 74-123.

Computer readable media include magnetically readable media, optically readable media, electronically readable media and magnetic/optical media. For example, the computer readable media may
40 be a hard disk, a floppy disk, a magnetic tape, CD-ROM, Digital Versatile Disk (DVD), Random Access Memory (RAM), or Read Only Memory (ROM) as well as other types of other media known to those skilled in the art.

Embodiments of the present invention include systems, particularly computer systems which store and manipulate the sequence information described herein. One example of a computer system 100 is
35 illustrated in block diagram form in Figure 6. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the nucleotide sequences of the cDNA codes of SEQ ID NOS. 24-73, or the amino acid sequences of the polypeptide codes

5 of SEQ ID NOS. 74-123. In one embodiment, the computer system 100 is a Sun Enterprise 1000 server (Sun Microsystems, Palo Alto, CA). The computer system 100 preferably includes a processor for processing, accessing and manipulating the sequence data. The processor 105 can be any well-known type of central processing unit, such as the Pentium III from Intel Corporation, or similar processor from Sun,
10 5 Motorola, Compaq or International Business Machines.

Preferably, the computer system 100 is a general purpose system that comprises the processor 105 and one or more internal data storage components 110 for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.
15

10 In one particular embodiment, the computer system 100 includes a processor 105 connected to a bus which is connected to a main memory 115 (preferably implemented as RAM) and one or more internal data storage devices 110, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system 100 further includes one or more data retrieving device 118 for reading the data stored on the internal data storage devices 110.
20

15 The data retrieving device 118 may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, etc. In some embodiments, the internal data storage device 110 is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, etc. containing control logic and/or data recorded thereon. The computer system 100 may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage
25 20 component once inserted in the data retrieving device.

The computer system 100 includes a display 120 which is used to display output to a computer user. It should also be noted that the computer system 100 can be linked to other computer systems 125a-c in a network or wide area network to provide centralized access to the computer system 100.
30

35 Software for accessing and processing the nucleotide sequences of the cDNA codes of SEQ ID NOS. 24-73, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 74-123 (such as search tools, compare tools, and modeling tools etc.) may reside in main memory 115 during execution.
25

In some embodiments, the computer system 100 may further comprise a sequence comparer for comparing the above-described cDNA codes of SEQ ID NOS. 24-73 or polypeptide codes of SEQ ID NOS. 74-123 stored on a computer readable medium to reference nucleotide or polypeptide sequences stored on
40 30 a computer readable medium. A "sequence comparer" refers to one or more programs which are implemented on the computer system 100 to compare a nucleotide or polypeptide sequence with other nucleotide or polypeptide sequences and/or compounds including but not limited to peptides, peptidomimetics, and chemicals stored within the data storage means. For example, the sequence
45 35 acid sequences of the polypeptide codes of SEQ ID NOS. 74-123 stored on a computer readable medium to reference sequences stored on a computer readable medium to identify homologies, motifs implicated in
50

5 biological function, or structural motifs. The various sequence comparer programs identified elsewhere in this patent specification are particularly contemplated for use in this aspect of the invention.

Figure 7 is a flow diagram illustrating one embodiment of a process 200 for comparing a new nucleotide or protein sequence with a database of sequences in order to determine the homology levels
10 5 between the new sequence and the sequences in the database. The database of sequences can be a private database stored within the computer system 100, or a public database such as GENBANK, PIR or SWISSPROT that is available through the Internet.

15 The process 200 begins at a start state 201 and then moves to a state 202 wherein the new sequence to be compared is stored to a memory in a computer system 100. As discussed above, the memory could be any type of memory, including RAM or an internal storage device.

20 The process 200 then moves to a state 204 wherein a database of sequences is opened for analysis and comparison. The process 200 then moves to a state 206 wherein the first sequence stored in the database is read into a memory on the computer. A comparison is then performed at a state 210 to determine if the first sequence is the same as the second sequence. It is important to note that this step is
25 not limited to performing an exact comparison between the new sequence and the first sequence in the database. Well-known methods are known to those of skill in the art for comparing two nucleotide or protein sequences, even if they are not identical. For example, gaps can be introduced into one sequence in order to raise the homology level between the two tested sequences. The parameters that control whether gaps or other features are introduced into a sequence during comparison are normally entered by the user of the
30 computer system.

35 Once a comparison of the two sequences has been performed at the state 210, a determination is made at a decision state 210 whether the two sequences are the same. Of course, the term "same" is not limited to sequences that are absolutely identical. Sequences that are within the homology parameters entered by the user will be marked as "same" in the process 200.

40 If a determination is made that the two sequences are the same, the process 200 moves to a state 214 wherein the name of the sequence from the database is displayed to the user. This state notifies the user that the sequence with the displayed name fulfills the homology constraints that were entered. Once the name of the stored sequence is displayed to the user, the process 200 moves to a decision state 218 wherein a determination is made whether more sequences exist in the database. If no more sequences
45 exist in the database, then the process 200 terminates at an end state 220. However, if more sequences do exist in the database, then the process 200 moves to a state 224 wherein a pointer is moved to the next sequence in the database so that it can be compared to the new sequence. In this manner, the new sequence is aligned and compared with every sequence in the database.

50 It should be noted that if a determination had been made at the decision state 212 that the sequences were not homologous, then the process 200 would move immediately to the decision state 218 in order to determine if any other sequences were available in the database for comparison.

5 Accordingly, one aspect of the present invention is a computer system comprising a processor, a
data storage device having stored thereon a nucleic acid code of SEQ ID NOS. 24-73 or a polypeptide code
of SEQ ID NOS. 74-123, a data storage device having retrievably stored thereon reference nucleotide
10 sequences or polypeptide sequences to be compared to the nucleic acid code of SEQ ID NOS. 24-73 or
5 polypeptide code of SEQ ID NOS. 74-123 and a sequence comparer for conducting the comparison. The
sequence comparer may indicate a homology level between the sequences compared or identify structural
motifs in the above described nucleic acid code of SEQ ID NOS. 24-73 and polypeptide codes of SEQ ID
NOS. 74-123 or it may identify structural motifs in sequences which are compared to these cDNA codes and
15 polypeptide codes. In some embodiments, the data storage device may have stored thereon the sequences
10 of at least 2, 5, 10, 15, 20, 25, 30, or 50 of the cDNA codes of SEQ ID NOS. 24-73 or polypeptide codes of
SEQ ID NOS. 74-123.

20 Another aspect of the present invention is a method for determining the level of homology between
a nucleic acid code of SEQ ID NOS. 24-73 and a reference nucleotide sequence, comprising the steps of
reading the nucleic acid code and the reference nucleotide sequence through the use of a computer
15 program which determines homology levels and determining homology between the nucleic acid code and
the reference nucleotide sequence with the computer program. The computer program may be any of a
25 number of computer programs for determining homology levels, including those specifically enumerated
herein, including BLAST2N with the default parameters or with any modified parameters. The method may
be implemented using the computer systems described above. The method may also be performed by
30 reading 2, 5, 10, 15, 20, 25, 30, or 50 of the above described cDNA codes of SEQ ID NOS. 24-73 through
use of the computer program and determining homology between the cDNA codes and reference nucleotide
sequences.

35 Figure 8 is a flow diagram illustrating one embodiment of a process 250 in a computer for
determining whether two sequences are homologous. The process 250 begins at a start state 252 and then
25 moves to a state 254 wherein a first sequence to be compared is stored to a memory. The second
sequence to be compared is then stored to a memory at a state 256. The process 250 then moves to a
state 260 wherein the first character in the first sequence is read and then to a state 262 wherein the first
40 character of the second sequence is read. It should be understood that if the sequence is a nucleotide
sequence, then the character would normally be either A, T, C, G or U. If the sequence is a protein
30 sequence, then it should be in the single letter amino acid code so that the first and sequence sequences
can be easily compared.

45 A determination is then made at a decision state 264 whether the two characters are the same. If
they are the same, then the process 250 moves to a state 268 wherein the next characters in the first and
second sequences are read. A determination is then made whether the next characters are the same. If
35 they are, then the process 250 continues this loop until two characters are not the same. If a determination
50 is made that the next two characters are not the same, the process 250 moves to a decision state 274 to
determine whether there are any more characters either sequence to read.

5 If there aren't any more characters to read, then the process 250 moves to a state 276 wherein the level of homology between the first and second sequences is displayed to the user. The level of homology is determined by calculating the profragment of characters between the sequences that were the same out of the total number of sequences in the first sequence. Thus, if every character in a first 100 nucleotide

10 5 sequence aligned with a every character in a second sequence, the homology level would be 100%.

Alternatively, the computer program may be a computer program which compares the nucleotide sequences of the cDNA codes of the present invention, to reference nucleotide sequences in order to determine whether the nucleic acid code of SEQ ID NOs. 24-73 differs from a reference nucleic acid sequence at one or more positions. Optionally such a program records the length and identity of inserted,

15 10 deleted or substituted nucleotides with respect to the sequence of either the reference polynucleotide or the nucleic acid code of SEQ ID NOs. 24-73. In one embodiment, the computer program may be a program which determines whether the nucleotide sequences of the cDNA codes of SEQ ID NOs. 24-73 contain a biallelic marker or single nucleotide polymorphism (SNP) with respect to a reference nucleotide sequence. This single nucleotide polymorphism may comprise a single base substitution, insertion, or deletion, while

20 15 this biallelic marker may comprise about one to ten consecutive bases substituted, inserted or deleted.

Another aspect of the present invention is a method for determining the level of homology between a polypeptide code of SEQ ID NOS. 74-123 and a reference polypeptide sequence, comprising the steps of reading the polypeptide code of SEQ ID NOS. 74-123 and the reference polypeptide sequence through use of a computer program which determines homology levels and determining homology between the

25 20 polypeptide code and the reference polypeptide sequence using the computer program.

Accordingly, another aspect of the present invention is a method for determining whether a nucleic acid code of SEQ ID NOs. 24-73 differs at one or more nucleotides from a reference nucleotide sequence comprising the steps of reading the nucleic acid code and the reference nucleotide sequence through use of a computer program which identifies differences between nucleic acid sequences and identifying differences

30 35 25 between the nucleic acid code and the reference nucleotide sequence with the computer program. In some embodiments, the computer program is a program which identifies single nucleotide polymorphisms. The method may be implemented by the computer systems described above and the method illustrated in Figure 8. The method may also be performed by reading at least 2, 5, 10, 15, 20, 25, 30, or 50 of the cDNA codes of SEQ ID NOs. 24-73 and the reference nucleotide sequences through the use of the computer program

40 30 and identifying differences between the cDNA codes and the reference nucleotide sequences with the computer program.

In other embodiments the computer based system may further comprise an identifier for identifying features within the nucleotide sequences of the cDNA codes of SEQ ID NOs. 24-73 or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 74-123.

35 50 An "identifier" refers to one or more programs which identifies certain features within the above-described nucleotide sequences of the cDNA codes of SEQ ID NOs. 24-73 or the amino acid sequences of

the polypeptide codes of SEQ ID NOS. 74-123. In one embodiment, the identifier may comprise a program which identifies an open reading frame in the cDNAs codes of SEQ ID NOS. 24-73.

Figure 9 is a flow diagram illustrating one embodiment of an identifier process 300 for detecting the presence of a feature in a sequence. The process 300 begins at a start state 302 and then moves to a state 304 wherein a first sequence that is to be checked for features is stored to a memory 115 in the computer system 100. The process 300 then moves to a state 306 wherein a database of sequence features is opened. Such a database would include a list of each feature's attributes along with the name of the feature. For example, a feature name could be "Initiation Codon" and the attribute would be "ATG". Another example would be the feature name "TAATAA Box" and the feature attribute would be "TAATAA". An example of such a database is produced by the University of Wisconsin Genetics Computer Group (www.gcg.com).

Once the database of features is opened at the state 306, the process 300 moves to a state 308 wherein the first feature is read from the database. A comparison of the attribute of the first feature with the first sequence is then made at a state 310. A determination is then made at a decision state 316 whether the attribute of the feature was found in the first sequence. If the attribute was found, then the process 300 moves to a state 318 wherein the name of the found feature is displayed to the user.

The process 300 then moves to a decision state 320 wherein a determination is made whether more features exist in the database. If no more features do exist, then the process 300 terminates at an end state 324. However, if more features do exist in the database, then the process 300 reads the next sequence feature at a state 326 and loops back to the state 310 wherein the attribute of the next feature is compared against the first sequence.

It should be noted, that if the feature attribute is not found in the first sequence at the decision state 316, the process 300 moves directly to the decision state 320 in order to determine if any more features exist in the database.

In another embodiment, the identifier may comprise a molecular modeling program which determines the 3-dimensional structure of the polypeptides codes of SEQ ID NOS. 74-123. In some embodiments, the molecular modeling program identifies target sequences that are most compatible with profiles representing the structural environments of the residues in known three-dimensional protein structures. (See, e.g., Eisenberg *et al.*, U.S. Patent No. 5,436,850 issued July 25, 1995). In another technique, the known three-dimensional structures of proteins in a given family are superimposed to define the structurally conserved regions in that family. This protein modeling technique also uses the known three-dimensional structure of a homologous protein to approximate the structure of the polypeptide codes of SEQ ID NOS. 74-123. (See e.g., Srinivasan, *et al.*, U.S. Patent No. 5,557,535 issued September 17, 1996). Conventional homology modeling techniques have been used routinely to build models of proteases and antibodies. (Sowdhamini *et al.*, Protein Engineering 10:207, 215 (1997)). Comparative approaches can also be used to develop three-dimensional protein models when the protein of interest has poor sequence identity to template proteins. In some cases, proteins fold into similar three-dimensional structures despite having

5 very weak sequence identities. For example, the three-dimensional structures of a number of helical cytokines fold in similar three-dimensional topology in spite of weak sequence homology.

10 The recent development of threading methods now enables the identification of likely folding patterns in a number of situations where the structural relatedness between target and template(s) is not detectable at the sequence level. Hybrid methods, in which fold recognition is performed using Multiple Sequence Threading (MST), structural equivalencies are deduced from the threading output using a distance geometry program DRAGON to construct a low resolution model, and a full-atom representation is constructed using a molecular modeling package such as QUANTA.

15 According to this 3-step approach, candidate templates are first identified by using the novel fold recognition algorithm MST, which is capable of performing simultaneous threading of multiple aligned sequences onto one or more 3-D structures. In a second step, the structural equivalencies obtained from the MST output are converted into inter-residue distance restraints and fed into the distance geometry program DRAGON, together with auxiliary information obtained from secondary structure predictions. The program combines the restraints in an unbiased manner and rapidly generates a large number of low resolution model confirmations. In a third step, these low resolution model confirmations are converted into full-atom models and subjected to energy minimization using the molecular modeling package QUANTA. (See e.g., Aszódi *et al.*, *Proteins: Structure, Function, and Genetics*, Supplement 1:38-42 (1997)).

20 The results of the molecular modeling analysis may then be used in rational drug design techniques to identify agents which modulate the activity of the polypeptide codes of SEQ ID NOS. 74-123.

25 Accordingly, another aspect of the present invention is a method of identifying a feature within the cDNA codes of SEQ ID NOS. 24-73 or the polypeptide codes of SEQ ID NOS. 74-123 comprising reading the nucleic acid code(s) or the polypeptide code(s) through the use of a computer program which identifies features therein and identifying features within the nucleic acid code(s) or polypeptide code(s) with the computer program. In one embodiment, computer program comprises a computer program which identifies open reading frames. In a further embodiment, the computer program identifies structural motifs in a polypeptide sequence. In another embodiment, the computer program comprises a molecular modeling program. The method may be performed by reading a single sequence or at least 2, 5, 10, 15, 20, 25, 30, or 50 of the cDNA codes of SEQ ID NOS. 24-73 or the polypeptide codes of SEQ ID NOS. 74-123 through the use of the computer program and identifying features within the cDNA codes or polypeptide codes with the computer program.

30 The cDNA codes of SEQ ID NOS. 24-73 or the polypeptide codes of SEQ ID NOS. 74-123 may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the cDNA codes of SEQ ID NOS. 24-73 or the polypeptide codes of SEQ ID NOS. 74-123 may be stored as text in a word processing file, such as MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE. In addition, many computer programs and databases may be used as sequence comparers, identifiers, or sources of reference nucleotide or polypeptide sequences to be compared to the cDNA codes of SEQ ID NOS. 24-73 or

the polypeptide codes of SEQ ID NOS. 74-123. The following list is intended not to limit the invention but to provide guidance to programs and databases which are useful with the cDNA codes of SEQ ID NOS. 24-73 or the polypeptide codes of SEQ ID NOS. 74-123. The programs and databases which may be used include, but are not limited to: MacPattern (EMBL), DiscoveryBase (Molecular Applications Group), GeneMine (Molecular Applications Group), Look (Molecular Applications Group), MacLook (Molecular Applications Group), BLAST and BLAST2 (NCBI), BLASTN and BLASTX (Altschul et al, *J. Mol. Biol.* 215: 403 (1990)), FASTA (Pearson and Lipman, *Proc. Natl. Acad. Sci. USA*, 85: 2444 (1988)), FASTDB (Brufag *et al. Comp. App. Biosci.* 6:237-245, 1990), Catalyst (Molecular Simulations Inc.), Catalyst/SHAPE (Molecular Simulations Inc.), Cerius².DBAccess (Molecular Simulations Inc.), HypoGen (Molecular Simulations Inc.), Insight II, (Molecular Simulations Inc.), Discover (Molecular Simulations Inc.), CHARMM (Molecular Simulations Inc.), Felix (Molecular Simulations Inc.), DelPhi, (Molecular Simulations Inc.), QuanteMM, (Molecular Simulations Inc.), Homology (Molecular Simulations Inc.), Modeler (Molecular Simulations Inc.), ISIS (Molecular Simulations Inc.), Quanta/Protein Design (Molecular Simulations Inc.), WebLab (Molecular Simulations Inc.), WebLab Diversity Explorer (Molecular Simulations Inc.), Gene Explorer (Molecular Simulations Inc.), SeqFold (Molecular Simulations Inc.), the EMBL/Swissprotein database, the MDL Available Chemicals Directory database, the MDL Drug Data Report data base, the Comprehensive Medicinal Chemistry database, Derwent's World Drug Index database, the BioByteMasterFile database, the Genbank database, and the Genseqn database. Many other programs and data bases would be apparent to one of skill in the art given the present disclosure.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn-helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

EXAMPLE 55

Methods of Making Nucleic Acids

The present invention also comprises methods of making the cDNA of SEQ ID Nos.24-73, genomic DNA obtainable therefrom, or fragment thereof. The methods comprise sequentially linking together nucleotides to produce the nucleic acids having the preceding sequences. A variety of methods of synthesizing nucleic acids are known to those skilled in the art.

In many of these methods, synthesis is conducted on a solid support. These included the 3' phosphoramidite methods in which the 3' terminal base of the desired oligonucleotide is immobilized on an insoluble carrier. The nucleotide base to be added is blocked at the 5' hydroxyl and activated at the 3' hydroxyl so as to cause coupling with the immobilized nucleotide base. Deblocking of the new immobilized nucleotide compound and repetition of the cycle will produce the desired polynucleotide. Alternatively, polynucleotides may be prepared as described in U.S. Patent No. 5,049,656. In some embodiments,

several polynucleotides prepared as described above are ligated together to generate longer polynucleotides having a desired sequence.

EXAMPLE 56

Methods of Making Polypeptides

The present invention also comprises methods of making the polynucleotides encoded by the cDNA of SEQ ID Nos.24-73, genomic DNA obtainable therefrom, or fragments thereof and methods of making the polypeptides of SEQ ID Nos.74-123 or fragments thereof. The methods comprise sequentially linking together amino acids to produce the nucleic polypeptides having the preceding sequences. In some embodiments, the polypeptides made by these methods are 150 amino acids or less in length. In other

embodiments, the polypeptides made by these methods are 120 amino acids or less in length.

A variety of methods of making polypeptides are known to those skilled in the art, including methods in which the carboxyl terminal amino acid is bound to polyvinyl benzene or another suitable resin. The amino acid to be added possesses blocking groups on its amino moiety and any side chain reactive groups so that only its carboxyl moiety can react. The carboxyl group is activated with carbodiimide or another activating agent and allowed to couple to the immobilized amino acid. After removal of the blocking group, the cycle is repeated to generate a polypeptide having the desired sequence. Alternatively, the methods described in U.S. Patent No. 5,049,656 may be used.

EXAMPLE 57

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, contigs were assembled for each of the cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases : Genbank (release 108), EMBL (release 58 and daily releases), Genseq (release 35.3) Swissprot (release 37), Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 53) and Swissprot (release 35). In some cases, based on

homology with other proteins, new open reading frames than the one previously selected were chosen. For example, the new open reading frame of SEQ ID NO: 27 does not contain a signal peptide anymore.

Then, the predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting at least 80% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues, which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (35 to 80% over the whole protein) indicating that the protein of the present invention is likely to have functions similar to those of the matched protein.

The third category contains proteins exhibiting homology to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features such as functional domains.

5 It should be noted that, in the numbering of amino acids in the protein sequences discussed below, in figures 10 to 13 and in Table V, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is
10 5 designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition, all amino acid sequences (SEQ ID NOs :74-123) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using
15 the Proscan software from the GCG package as follows.

10 The polypeptides encoded by the cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences that are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat located at <http://expasy.hcuge.ch/sprot/prosite.html>. Prosite_convert and prosite_scan programs
20 (http://ulrec3.unil.ch/ftpserveur/prosite_scan) were used to find signatures on the cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of
25 the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native
30 (unshuffled) proteins was used as an index. Every pattern for which the ratio was greater than 20% (one hit on shuffled proteins for 5 hits on native proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite_statistics) are available on the ftp site
35 http://ulrec3.unil.ch/ftpserveur/prosite_scan.

25 *A) Proteins which are closely related to known proteins*

Protein of SEQ ID NO: 76 (internal designation 105-095-1-0-D10-FLC)

The protein of SEQ ID NO: 76 encoded by the cDNA of SEQ ID NO:26 exhibits identity to the
40 human parotid secretory protein HPSP (Genseq accession number W60682 and SEQ ID NO : 124) as shown by the alignment of figure 10. Antagonists of this protein may be used to treat cancer and
30 autoimmune diseases particularly of secretory or gastrointestinal tissue.

Taken together, these data suggest that the protein of SEQ ID NO: 76 or part thereof may play a
45 role in cell differentiation and/or proliferation. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to cancer and autoimmune diseases.

Protein of SEQ ID NO: 93 (internal designation 117-007-2-0-C4-FLC)

35 The protein of SEQ ID NO: 93 encoded by the cDNA of SEQ ID NO:43 exhibits identity to a human protein thought to be transmembraneous (Genseq accession number W88491 and SEQ ID NO : 125) as
50 shown by the alignment of figure 11. This protein displays homology to alpha-2-HS glycoprotein precursors

(fetuins) of human and pigs, which belong to the cystatin superfamily. The 382-amino-acid-long protein of SEQ ID NO: 93, which is similar in size to fetuins, displays a cystatin-like domain with 12 conserved cysteines (positions 36, 93, 104, 117, 137, 151, 154, 216, 224, 237, 254 and 368, in bold in figure 11) and a conserved region around the second cysteine (positions 89 to 96, underlined in figure 11) although the typical PROSITE signatures for fetuins is not present. In addition, the potential active site QxVxG is also present in the protein of the invention (positions 198 to 202, in italics in figure 11). The cystatin superfamily contain evolutionarily related proteins with diverse functions such as cysteine protease inhibitors, stefins, fetuins and kininogens (see review by Brown and Dziegielewska, *Prot. Science*, 6:5-12 (1997)).

Taken together, these data suggest that the protein of SEQ ID NO: 93 or part thereof may play a role in cellular proteolysis, maybe as a protease inhibitor. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, and especially tumor progression and metastasis, chronic inflammation, neurodegenerative diseases such as Alzheimer disease, diabetes, hypertension and immune disorders. It may also be useful in treating patients with cardiovascular disorders by modulating their blood coagulation properties.

15 Protein of SEQ ID NO: 75 (internal designation 105-031-3-0-D6-FLC)

The protein of SEQ ID NO: 75 encoded by the cDNA of SEQ ID NO: 25 exhibits homology to a murine putative sialyltransferase protein (TREMBL accession number O88725 and SEQ ID NO: 126) as shown by the alignment of figure 12. Sialyltransferases are type II transmembrane proteins involved in the biosynthesis of sialosides which are important in a large variety of biological processes such as cell-cell communication, cell-matrix interactions, maintenance of serum glycoproteins in the circulation, and so on (Sjoberg *et al.*, *J. Biol. Chem.* 271:7450-7459 (1996); Tsuji, *J. Biochem.* 120:1-13 (1996)). The protein of SEQ ID NO: 75 displays the two conserved motifs of the sialyltransferase protein family, namely the centrally located sialylmotifL (positions 73 to 120, in bold in figure 12) thought to be involved in the recognition of the sugar nucleotide donor common to all sialyltransferases and the sialylmotifS (positions 211 to 233, in italics in figure 12) thought to be the catalytic site and located in the C-terminus of the protein. Furthermore, the 302-amino-acid long protein of SEQ ID NO: 75 has a size similar to the one of the members of the sialyltransferase family. In addition, the protein of the invention has a predicted transmembrane structure. Indeed, it contains 2 potential transmembrane segment (positions 7 to 27 and 206 to 226, underlined in figure 12) as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 75 or part thereof may play a role in the biosynthesis of sialyl-glycoconjugates, probably as a sialyltransferase. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, cystic fibrosis and hypothyroidism.

5 Proteins of SEQ ID NOs: 104 (internal designation 108-008-5-O-C5-FL)

The protein of SEQ ID NO: 104 encoded by the cDNA of SEQ ID NO: 54 exhibits extensive homology over the whole length of the murine recombination activating gene 1 inducing protein (Genbank accession number X96618 and SEQ ID NO: 177). As shown by the alignment of figure 13, the amino acid
10 residues are identical except for the positions 6, 7, 10-13, 17, 25, 34-35, 42, 51, 56, 62, 68, 71, 74, 78, 91, 93, 95-96, 106, 121-122, 151-152, 159, 162-163, 170-171, 176-177, 188, 190, 192, 196, 199, 202-203, 206, 210, 215 and 217 of the 221 amino acid long matched protein. This protein with 4 potential transmembrane segments is involved in the induction of the recombination of V(D)J segments in T cells (Muraguchi *et al*,
15 *Leuk Lymphoma*, 30 :73-85 (1998)).

10 Taken together, these data suggest that the protein of SEQ ID NO: 104 may play a role in lymphocyte repertoire formation. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, immunological disorders and inflammatory disorders. It may also be useful to modulate the inflammatory or immune response to infectious agents, such as HIV.

20 B) *Proteins which are remotely related to proteins with known functions*

Proteins of SEQ ID NO: 87 (internal designation 116-073-4-0-C8-FLC)

25 Part of the protein of SEQ ID NO: 87 encoded by the cDNA of SEQ ID NO:37 shows homology over the whole length of the widely conserved family of lysozyme C precursors (fish, bird, and mammals). In addition, this protein displays the characteristic alpha-lactalbumin/lysozyme C PROSITE signature of this
30 family of glycosyl hydrolases, family 22 (positions 162 to 180, see Table V). Lysozymes C are bacteriolytic defensive enzymes and alpha-lactalbumin is the regulatory subunit of lactose synthetase. Lysozymes C and alpha-lactalbumin appear to be evolutionary related (Qasba and Kumar, *Crit. Rev. Biochem. Mol. Biol.* 32:255-306 (1997)).

35 Taken together, these data suggest that the protein of SEQ ID NO: 87 or part thereof, especially the domain matching the above mentioned lysozyme C precursors, may play a role in glycoprotein and/or peptidoglycan metabolism, probably as a glycosyl hydrolase. Thus, this protein or part thereof, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer and amyloidosis. It
40 may also be useful in modulating defensive responses to infectious agents such as bacteria.

Proteins of SEQ ID NO: 86 (internal designation 116-054-3-0-G12-FLC)

30 The protein of SEQ ID NO: 86 encoded by the cDNA of SEQ ID NO:36 found in liver shows homology to the MLRQ subunit of NADH-ubiquinone oxidoreductase (complex I) of bovine, murine and human species (Genbank accession numbers X64897, U59509 and EMBL accession number U94586
45 respectively). In addition, the 83-amino-acid-long protein of SEQ ID NO: 86 has a size similar to those of known MLRQ subunits. Complex I is part of the mitochondrial electron transport chain and is involved in the
50 dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high-energy demand such as brain (mental retardation,

convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (ophthalmoplegia, ptosis, cataract and retinopathy). For a review on complex I, see Smeitink *et al.*, *Hum. Mol. Genet.*, **7** : 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 86 may be a NADH-ubiquinone oxidoreductase MLRQ-like protein. Thus, this protein or part thereof, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders (ophthalmoplegia, ptosis, cataract and retinopathy).

Protein of SEQ ID NO: 91 (internal designation 117-005-4-0-E5-FLC)

The protein of SEQ ID NO:91 encoded by the cDNA of SEQ ID NO:41 found in liver shows homology over domains of a family of mitochondrial substrate carrier proteins found in the inner mitochondrial membrane. These carrier proteins are evolutionary related and consist of three tandem repeats of a domain of approximately one hundred residues with each of these domains containing two transmembrane regions. The 308-amino-acid-long protein of SEQ ID NO:91 has a size similar to the one of mitochondrial carrier proteins and displays the characteristic PROSITE signature of this protein family three times (positions 19 to 28, 115 to 124 and 237 to 246, see Table V). In addition, the protein of SEQ ID NO: 91 has 6 potential transmembrane segments of 20 amino acids, 4 being predicted with a high level of confidence (positions 1-21, 54-74, 135-155 and 217-237) and 2 with a lower level of confidence (positions 96-116 and 191-211), using the TopPred II software (Claros and von Heijne, *CABIOS applic. Notes*, **10** :685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 91 or part thereof may play a role in energy transfer, probably as a mitochondrial substrate carrier protein. Thus, this protein or part thereof, may be useful in diagnosing and/or treating several disorders including, but not limited to, mitochondriopathies and obesity.

In particular, the protein of SEQ ID NO: 91 encoded by the cDNA of SEQ ID NO: 41 exhibits homology to apolipoprotein A-IV related protein. Lipoproteins such as HDL and LDL contain characteristic apolipoproteins that are responsible for targeting them to certain tissues and for activating enzymes required for the trafficking of the lipid fraction of the lipoprotein (including cholesterol). Apolipoprotein A-IV-related protein (AAARP) is a member of the apolipoprotein family; it is 52% similar (29% identical) to Apolipoprotein A-IV (ApoA-IV) and therefore is likely to have a similar function. ApoA-IV is found associated with the chylomicron and HDL fraction of blood. Its specific function is currently unknown; however, it is expressed in the liver and intestine and regulated by high fat meals (upregulated) and by leptin (downregulated). Levels of ApoA-IV are correlated with glycemic control in young type I diabetes (IDDM) patients. Over-expression of the protein is protective against atherosclerosis in mice with ApoE knockouts. Finally, ApoAIV is responsible

for part of the inter-individual variability in blood cholesterol response to changes in dietary fat/cholesterol intake.

AA4RP circulates in the blood, and is therefore easily amenable to therapeutic intervention, by direct administration into the blood of synthetic peptide analogs that mimic its activity or function as competitive antagonists (dominant negatives). Since this protein is involved in fat transport and in cholesterol trafficking within the body and mediates the changes in blood cholesterol in response to dietary changes, interventions targeted at this protein will be useful for cholesterol lowering and anti-atherosclerosis therapeutics, and in the control of diabetes and obesity.

Proteins of SEQ ID NO: 74 (internal designation 105-016-3-0-E3-FLC)

The 325-amino-acid-long protein of SEQ ID NO: 74 encoded by the cDNA of SEQ ID NO: 24 shows homology over the whole length of the 332-amino-acid-long murine neural proliferation differentiation and control 1 protein or NPDC-1 (Genbank accession number X67209) which is thought to play an important role in the control of neural cell proliferation and differentiation as well as in cell survival probably by interacting directly or not with cell cycle regulators such as E2F-1 (Galiana *et al.*, *Proc. Natl. Acad. Sci. USA* 92:1560-1564 (1995); Dupont *et al.*, *J. Neurosci. Res.* 51:257-267 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 74 or part thereof may play a role in cell proliferation and differentiation. Thus, this protein or part thereof, may be useful in diagnosing and/or treating several disorders including, but not limited to cancer and neurodegenerative disorders.

Protein of SEQ ID NO: 111 (internal designation 108-013-5-0-H9-FL)

The protein of SEQ ID NO: 111 encoded by the extended cDNA SEQ ID NO: 61 shows homologies with a family of lysophospholipases conserved among eukaryotes (yeast, rabbit, rodents and human). In addition, some members of this family (rat :Genbank accession number U97146, rabbit : Genbank accession number U97147) exhibit a calcium-independent phospholipase A2 activity (Portilla *et al.*, *J. Am. Soc. Nephrol.*, 9:1178-1186 (1998)). All members of this family exhibit the active site consensus GXSXG motif of carboxylesterases that is also found in the protein of the invention (position 54 to 58). In addition, this protein may be a membrane protein with one transmembrane domain as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 :685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO:111 may play a role in fatty acid metabolism, probably as a phospholipase. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, diabetes. It may also be useful in modulating inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEQ ID NOs:101 (internal designation 108-005-5-0-F9-FL)

The protein of SEQ ID NO:71 encoded by the extended cDNA SEQ ID NO: 51 shows homology with the *Drosophila* rhythmically expressed gene 2 protein (Genbank accession number U65492). Expression of the mRNA coding for the matched protein is dependent on the interplay between light-dark

5 cycle, feeding conditions and expression of the *per* gene which is essential to the function of the endogenous circadian pacemaker (Van Gelder *et al.*, *Curr. Biol.*, 5:1424-1436 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 101 may play a role in circadian control. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, insomnia, depression, stress and other disorders of the circadian rhythm. In addition, such a protein may be useful in modulating the physiological response to night work or to jet lag.

C) *Proteins homologous to a domain of a protein with known function*

Protein of SEQ ID NO: 94 (internal designation 121-004-3-0-F6-FLC)

15 The protein of SEQ ID NO: 94 encoded by the cDNA of SEQ ID NO:44 found in brain shows
20 homology to a ganglioside-induced differentiation associated protein 1 found in both human (EMBL accession number 075786) and murine species (EMBL accession number 088741). Gangliosides are believed to be involved in neural cell development, differentiation, survival and pathology, maybe as modulators of membrane properties (Brigande and Seyfried, *Ann. N. Y. Acad. Sci.* 845:215-218 (1998); Schengrund and Mummert, *Ann. N. Y. Acad. Sci.* 845:278-284 (1998)).

25 Taken together, these data suggest that the protein of SEQ ID NO: 94 or part thereof may play a role in central nervous system development and differentiation. Thus, this protein or part thereof, may be useful in diagnosing and treating several disorders including, but not limited to, cancer and neuronal disorders.

Protein of SEQ ID NO: 89 (internal designation 117-005-2-0-E10-FLC)

30 The protein of SEQ ID NO: 89 encoded by the cDNA of SEQ ID NO:39 shows remote homology to domains of apolipoprotein A-IV of human, murine and chicken species (Genbank accession numbers M13654, M13966, and EMBL accession number O93601 respectively). These apolipoproteins are thought to play a role in chylomicrons and VLDL secretion and catabolism and may also be involved in reverse cholesterol transport. In addition, the 366-amino-acid-long protein of SEQ ID NO: 89 has a size similar to
35 those of above-mentioned apolipoprotein A-IV.

The protein of SEQ ID NO: 89 encoded by the cDNA of SEQ ID NO: 39 exhibits homology to the carnitine carrier related protein. The carnitine carrier-related protein (CCRP) is 45% similar (30% identical) to the acyl-carnitine/carnitine carrier and is therefore likely to have a similar function. The acyl-carnitine/carnitine carrier is a mitochondrial carrier protein that is responsible for transporting fatty acids into
40 the mitochondrion where they may be oxidized to produce energy. CCRP also shares underlying structural similarities with the uncoupling protein (UCP-1), another mitochondrial transporter protein which is involved in weight regulation and temperature homeostasis. UCP protein activity is regulated by nucleotides via a 9 amino acid protein domain that is relatively well conserved in the predicted CCR protein (6 of 9 identical, 9 of 9 similar), compared to only 4 of 9 for the acyl-carnitine/carnitine carrier itself. Therefore the function of the
45 CCRP may be amenable to direct activation or inhibition via small molecule nucleotide analogs.

50 Acyl-carnitine/carnitine carrier is required for transport of fatty acids into mitochondria before they can be oxidized for energy, however genetic mutations of this gene do not result in disturbances of weight.

5 This indicates that another protein must also be available for fatty acid transport, and CCRP is likely to be this transporter.

10 The rate of lipid burning by the mitochondrion is dependent upon the rate of delivery of fatty acids into the mitochondrion by these transporters. Regulation of the activity of CCRP, via its nucleotide binding domain or by other interventions to increase its availability or activity in the mitochondria, would increase the fat burning capacity of tissues. Since elevated plasma free fatty acids have been implicated in the causation of type II diabetes (NIDDM) such interventions could be designed to increase net clearance of lipids from the blood. Other effects of therapeutics targeted at CCRP could be to increase fat burning by liver and muscle at the expense of fat storage by adipose tissue, with the result of decreasing weight.

15 Taken together, these data suggest that the protein of SEQ ID NO: 89 may play a role in lipid metabolism. Thus, this protein or part thereof, may be useful in diagnosing and treating several disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, neurodegenerative disorders such as Alzheimer's disease or dementia, and obesity.

20 Protein of SEQ ID NO: 95 (internal designation 122-005-2-0-F11-FLC)

25 The protein of SEQ ID NO: 95 encoded by the cDNA of SEQ ID NO:45 exhibits homology with domains of a family of reductases, and especially with the NADH-cytochrome b5 reductase of rat, bovine and human species (Genbank accession numbers J03867, M83104 and Y09501, respectively). The homology include the flavin-adenine dinucleotide-binding domain of NADH-cytochrome b5 reductase proteins which belong to a flavoenzyme family whose members are involved in photosynthesis, in the assimilation of nitrogen and sulfur, in fatty-acid oxidation, in the reduction of methemoglobin and in the metabolism of many pesticides, drugs and carcinogens.

30 Taken together, these data suggest that the protein of SEQ ID NO: 95 may play a role in cellular oxidoreduction reactions, maybe as a flavoenzyme reductase. Thus, this protein or part thereof, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, methemoglobinemia, hyperlipidemia, obesity and cardiovascular disorders. It may also be useful in regulating the metabolism of pesticides, drugs and carcinogens.

35 Protein of SEQ ID NO: 106 (internal designation 108-011-5-O-B12-FL)

40 The protein of SEQ ID NO: 106 encoded by the extended cDNA SEQ ID NO: 56 shows homology to the predicted extracellular domain and part of transmembrane domain of interleukin-17 receptor of both human and murine species (Genbank accession numbers W04185 and W04184). These IL-17R proteins are thought to belong to a new family of receptors for cytokines which induce T cell proliferation, I-CAM expression and preferential maturation of haematopoietic precursors into neutrophils (Yao *et al.*, *Cytokine.*, 9:794-8001 (1997)). It is also thought to play a proinflammatory role and to induce nitric oxide. The protein of the invention has a 21 amino acid transmembrane domain (positions 172 to 192) as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)) matching the 21 amino acid putative transmembrane domain of human interleukin-17 receptor.

5 Taken together, these data suggest that the protein of SEQ ID NO: 106 may play a role in regulating immune and/or inflammatory responses. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological disorders, septic shock and impotence. In addition, this protein may also be useful to modulate immune and/or
10 inflammatory responses to infectious responses and/or to suppress graft rejection.

Protein of SEQ ID NO: 114 (internal designation 108-014-5-O-D12-FL)

15 The protein of SEQ ID NO: 114 encoded by the extended cDNA SEQ ID NO: 64 possess a cysteine-rich C3H2C3 region also found in G1 protein of *Drosophila melanogaster* (Swissprot accession number Q06003). This cysteine-rich region is similar to a RING type zinc finger, a domain that binds two
20 atoms of zinc and is probably involved in mediating protein-protein interaction.

Taken together, these data suggest that the protein of SEQ ID NO: 114 may play a role in protein-protein interaction.

20 The nucleic acid sequences of SEQ ID NOs: 24-73 or fragments thereof may also be used to construct fusion proteins in which the polypeptide sequences of SEQ ID NOs: 74-123 or fragments thereof
25 are fused to heterologous polypeptides. For example, the fragments of the polypeptides of SEQ ID NOs. 74-123 which are included in the fusion proteins may comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of the polypeptides of SEQ ID NOs. 74-123 or may be of any length suitable for the intended purpose of the fusion protein. Nucleic acids encoding the desired fusion protein are produced by cloning a nucleic acid of SEQ ID NOs. 24-73 in frame with a nucleic acid encoding the
30 heterologous polypeptide. The nucleic acid encoding the desired fusion protein is operably linked to a promoter in an appropriate vector, such as any of the vectors described above, and introduced into a host capable of expressing the fusion protein.

35 Antibodies against the polypeptides of SEQ ID NOs. 74-123 or fragments thereof may be used in immunoaffinity chromatography to isolate the polypeptides of SEQ ID NOs. 74-123 or fragments thereof or to
25 isolate fusion proteins containing the polypeptides of SEQ ID NOs. 74-123 or fragments thereof.

EXAMPLE 58

Immunoaffinity Chromatography

40 Antibodies prepared as described above are coupled to a support. Preferably, the antibodies are monoclonal antibodies, but polyclonal antibodies may also be used. The support may be any of those typically
30 employed in immunoaffinity chromatography, including Sepharose CL-4B (Pharmacia, Piscataway, NJ), Sepharose CL-2B (Pharmacia, Piscataway, NJ), Affi-gel 10 (Biorad, Richmond, CA), or glass beads.

45 The antibodies may be coupled to the support using any of the coupling reagents typically used in immunoaffinity chromatography, including cyanogen bromide. After coupling the antibody to the support, the support is contacted with a sample which contains a target polypeptide whose isolation, purification or
35 enrichment is desired. The target polypeptide may be a polypeptide of SEQ ID NOs. 74-123, a fragment thereof, or a fusion protein comprising a polypeptide of SEQ ID NOs. 74-123 or a fragment thereof.

5 Preferably, the sample is placed in contact with the support for a sufficient amount of time and under appropriate conditions to allow at least 50% of the target polypeptide to specifically bind to the antibody coupled to the support.

10 Thereafter, the support is washed with an appropriate wash solution to remove polypeptides which have non-specifically adhered to the support. The wash solution may be any of those typically employed in immunoaffinity chromatography, including PBS, Tris-lithium chloride buffer (0.1M lysine base and 0.5M lithium chloride, pH 8.0), Tris-hydrochloride buffer (0.05M Tris-hydrochloride, pH 8.0), or Tris/Triton/NaCl buffer (50mM Tris.cl, pH 8.0 or 9.0, 0.1% Triton X-100, and 0.5MNaCl).

15 After washing, the specifically bound target polypeptide is eluted from the support using the high pH or low pH elution solutions typically employed in immunoaffinity chromatography. In particular, the elution solutions may contain an eluant such as triethanolamine, diethylamine, calcium chloride, sodium thiocyanate, potassium bromide, acetic acid, or glycine. In some embodiments, the elution solution may also contain a detergent such as Triton X-100 or octyl- β -D-glucoside.

20 As discussed above, the cDNAs of the present invention or fragments thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris *et al.*, Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

30 The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding

occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

TABLE I

Id	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
24	153/1127	153/230	231/1127	1128	1415/1420	1434/1450
25	261/1166	261/314	315/1166	1167	-	1524/1556
26	67/813	67/111	112/813	814	1023/1028	1042/1058
27	187/438	-	187/438	439	612/617	632/648
28	92/1753	92/130	131/1753	1754	2070/2075	2090/2104
29	144/440	144/287	288/440	441	457/462	500/515
30	174/443	174/269	270/443	444	623/628	647/661
31	55/399	55/192	193/399	400	654/659	680/694
32	90/287	90/146	147/287	288	1078/1083	1096/1110
33	49/447	49/111	112/447	448	579/584	602/623
34	199/618	199/408	409/618	619	626/631	643/657
35	271/969	271/366	367/969	970	1092/1097	1123/1137
36	192/440	192/278	279/440	441	590/595	622/636
37	59/703	59/181	182/703	704	783/788	804/818
38	139/1389	139/198	199/1389	1390	1854/1859	1873/1888
39	21/1118	21/89	90/1118	1119	1858/1863	1879/1894
40	143/592	143/277	278/592	593	1877/1882	1899/1913
41	76/999	76/279	280/999	1000	1711/1716	1729/1744
42	123/464	123/269	270/464	465	908/913	931/946
43	85/1230	85/129	130/1230	1231	1589/1594	1607/1622
44	29/664	29/619	620/664	665	657/662	699/715
45	18/878	18/95	96/878	879	1500/1505	1533/1549
46	73/1008	73/147	148/1008	1009	1286/1291	1312/1328
47	165/842	165/251	252/842	843	1474/1479	1500/1515
48	31/1248	31/135	136/1248	1249	1580/1585	1607/1622
49	131/490	131/301	302/490	491	1411/1416	1434/1448
50	61/690	61/168	169/690	691	858/863	879/894
51	501/1253	501/1229	1230/1253	1254	1392/1397	1432/1447
52	25/402	25/96	97/402	403	1500/1505	1525/1540
53	280/678	280/411	412/678	679	1606/1611	1628/1643

Id	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
54	64/726	64/147	148/726	727	1279/1284	1300/1314
55	42/1097	42/110	111/1097	1098	2323/2328	2341/2356
56	245/1399	245/796	797/1399	1400	1669/1674	1687/1701
57	235/441	235/303	304/441	442	-	758/772
58	88/411	88/234	235/411	412	938/943	964/987
59	129/452	129/212	213/452	453	1290/1295	1309/1324
60	238/612	238/348	349/612	613	1885/1890	1905/1918
61	229/735	229/492	493/735	736	816/821	841/852
62	168/413	168/335	336/413	414	684/689	708/726
63	100/852	100/159	160/852	853	998/1003	1019/1039
64	238/1152	238/339	340/1152	1153	1298/1303	1324/1355
65	187/369	187/312	313/369	370	489/494	558/572
66	121/459	121/165	166/459	460	497/502	521/535
67	34/336	34/123	124/336	337	536/541	556/572
68	119/409	119/388	389/409	410	769/774	789/804
69	232/534	232/306	307/534	535	595/600	615/629
70	140/595	140/442	443/595	596	630/635	655/669
71	32/658	32/289	290/658	659	936/941	959/973
72	14/280	14/76	77/280	281	-	776/791
73	93/290	93/149	150/290	291	1078/1083	1096/1110

TABLE II

Id	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
74	-26 through 299	-26 through -1	1 through 299
75	-18 through 284	-18 through -1	1 through 284
76	-15 through 234	-15 through -1	1 through 234
77	1 through 84	-	1 through 84
78	-13 through 541	-13 through -1	1 through 541
79	-48 through 51	-48 through -1	1 through 51
80	-32 through 58	-32 through -1	1 through 58
81	-46 through 69	-46 through -1	1 through 69
82	-19 through 47	-19 through -1	1 through 47
83	-21 through 112	-21 through -1	1 through 112
84	-70 through 70	-70 through -1	1 through 70
85	-32 through 201	-32 through -1	1 through 201
86	-29 through 54	-29 through -1	1 through 54
87	-41 through 174	-41 through -1	1 through 174
88	-20 through 397	-20 through -1	1 through 397
89	-23 through 343	-23 through -1	1 through 343
90	-45 through 105	-45 through -1	1 through 105
91	-68 through 240	-68 through -1	1 through 240
92	-49 through 65	-49 through -1	1 through 65
93	-15 through 367	-15 through -1	1 through 367
94	-197 through 15	-197 through -1	1 through 15
95	-26 through 261	-26 through -1	1 through 261
96	-25 through 287	-25 through -1	1 through 287
97	-29 through 197	-29 through -1	1 through 197
98	-35 through 371	-35 through -1	1 through 371
99	-57 through 63	-57 through -1	1 through 63
100	-36 through 174	-36 through -1	1 through 174
101	-243 through 8	-243 through -1	1 through 8
102	-24 through 102	-24 through -1	1 through 102
103	-44 through 89	-44 through -1	1 through 89
104	-28 through 193	-28 through -1	1 through 193

Id	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
105	-23 through 329	-23 through -1	1 through 329
106	-184 through 201	-184 through -1	1 through 201
107	-23 through 46	-23 through -1	1 through 46
108	-49 through 59	-49 through -1	1 through 59
109	-28 through 80	-28 through -1	1 through 80
110	-37 through 88	-37 through -1	1 through 88
111	-88 through 81	-88 through -1	1 through 81
112	-56 through 26	-56 through -1	1 through 26
113	-20 through 231	-20 through -1	1 through 231
114	-34 through 271	-34 through -1	1 through 271
115	-42 through 19	-42 through -1	1 through 19
116	-15 through 98	-15 through -1	1 through 98
117	-30 through 71	-30 through -1	1 through 71
118	-90 through 7	-90 through -1	1 through 7
119	-25 through 76	-25 through -1	1 through 76
120	-101 through 51	-101 through -1	1 through 51
121	-86 through 123	-86 through -1	1 through 123
122	-21 through 68	-21 through -1	1 through 68
123	-19 through 47	-19 through -1	1 through 47

TABLE III

Id	Positions of preferred fragments
24	1-126, 164-259, 420-432, 1404-1450
25	32-44, 4199-1556
26	1-19, 1011-1058
27	1-16, 108-159, 595-648
28	1-119, 486-665, 1968-2009, 2055-2104
29	424-435, 500-515
30	1-122, 242-661
31	1-16, 649-694
32	1-663, 1070-110
33	1-129, 541-623
34	1-200, 614-657
35	1-419, 1094-1137
36	1-127, 323-331, 595-636
37	804-818
38	1-47, 438-611, 1005-1133, 1846-1888
39	1-430, 527-1894
40	1-119, 1743-1792, 1866-1913
41	1-70, 133-1235, 1729-1744
42	575-615, 896-946
43	513-526, 950-960, 1577-1622
44	1-2, 210-265, 674-715
45	1400-1441, 1508-1549
46	1-4, 1284, 1328

TABLE IV

Internal designation	Id	Type of sequence
105-016-3-0-E3-FL	24	DNA
105-031-3-0-D6-FL	25	DNA
105-095-1-0-D10-FL	26	DNA
105-118-4-0-E6-FL	27	DNA
114-025-2-0-F11-FL	28	DNA
116-005-4-0-G11-FL	29	DNA
116-032-2-0-F9-FL	30	DNA
116-047-3-0-B1-FL	31	DNA
116-048-4-0-A6-FL	32	DNA
116-049-1-0-F2-FL	33	DNA
116-050-2-0-A11-FL	34	DNA
116-054-3-0-E6-FL	35	DNA
116-054-3-0-G12-FL	36	DNA
116-073-4-0-C8-FL	37	DNA
117-002-3-0-G3-FL	38	DNA
117-005-2-0-E10-FL	39	DNA
117-005-3-0-F2-FL	40	DNA
117-005-4-0-E5-FL	41	DNA
117-007-2-0-B5-FL	42	DNA
117-007-2-0-C4-FL	43	DNA
121-004-3-0-F6-FL	44	DNA
122-005-2-0-F11-FL	45	DNA
122-007-3-0-D10-FL	46	DNA
108-004-5-0-B12-FL	47	DNA
108-004-5-0-C10-FL	48	DNA
108-004-5-0-G10-FL	49	DNA
108-005-5-0-D4-FL	50	DNA
108-005-5-0-F9-FL	51	DNA
108-006-5-0-C7-FL	52	DNA
108-006-5-0-E1-FL	53	DNA
108-008-5-0-C5-FL	54	DNA
108-008-5-0-G5-FL	55	DNA
108-011-5-0-B12-FL	56	DNA

Internal designation	Id	Type of sequence
108-011-5-0-C7-FL	57	DNA
108-011-5-0-G8-FL	58	DNA
108-011-5-0-H2-FL	59	DNA
108-013-5-0-G5-FL	60	DNA
108-013-5-0-H9-FL	61	DNA
108-014-5-0-A10-FL	62	DNA
108-014-5-0-C7-FL	63	DNA
108-014-5-0-D12-FL	64	DNA
108-014-5-0-H8-FL	65	DNA
108-015-5-0-E2-FL	66	DNA
108-016-5-0-C12-FL	67	DNA
108-016-5-0-D4-FL	68	DNA
108-019-5-0-F10-FL	69	DNA
108-019-5-0-F5-FL	70	DNA
108-019-5-0-H3-FL	71	DNA
108-020-5-0-D4-FL	72	DNA
108-020-5-0-E3-FL	73	DNA
105-016-3-0-E3-FL	74	PRT
105-031-3-0-D6-FL	75	PRT
105-095-1-0-D10-FL	76	PRT
105-118-4-0-E6-FL	77	PRT
114-025-2-0-F11-FL	78	PRT
116-005-4-0-G11-FL	79	PRT
116-032-2-0-F9-FL	80	PRT
116-047-3-0-B1-FL	81	PRT
116-048-4-0-A6-FL	82	PRT
116-049-1-0-F2-FL	83	PRT
116-050-2-0-A11-FL	84	PRT
116-054-3-0-E6-FL	85	PRT
116-054-3-0-G12-FL	86	PRT
116-073-4-0-C8-FL	87	PRT
117-002-3-0-G3-FL	88	PRT
117-005-2-0-E10-FL	89	PRT
117-005-3-0-F2-FL	90	PRT
117-005-4-0-E5-FL	91	PRT

Internal designation	Id	Type of sequence
117-007-2-0-B5-FL	92	PRT
117-007-2-0-C4-FL	93	PRT
121-004-3-0-F6-FL	94	PRT
122-005-2-0-F11-FL	95	PRT
122-007-3-0-D10-FL	96	PRT
108-004-5-0-B12-FL	97	PRT
108-004-5-0-C10-FL	98	PRT
108-004-5-0-G10-FL	99	PRT
108-005-5-0-D4-FL	100	PRT
108-005-5-0-F9-FL	101	PRT
108-006-5-0-C7-FL	102	PRT
108-006-5-0-E1-FL	103	PRT
108-008-5-0-C5-FL	104	PRT
108-008-5-0-G5-FL	105	PRT
108-011-5-0-B12-FL	106	PRT
108-011-5-0-C7-FL	107	PRT
108-011-5-0-G8-FL	108	PRT
108-011-5-0-H2-FL	109	PRT
108-013-5-0-G5-FL	110	PRT
108-013-5-0-H9-FL	111	PRT
108-014-5-0-A10-FL	112	PRT
108-014-5-0-C7-FL	113	PRT
108-014-5-0-D12-FL	114	PRT
108-014-5-0-H8-FL	115	PRT
108-015-5-0-E2-FL	116	PRT
108-016-5-0-C12-FL	117	PRT
108-016-5-0-D4-FL	118	PRT
108-019-5-0-F10-FL	119	PRT
108-019-5-0-F5-FL	120	PRT
108-019-5-0-H3-FL	121	PRT
108-020-5-0-D4-FL	122	PRT
108-020-5-0-E3-FL	123	PRT

TABLE V

Id	Locations	PROSITE signature Name
87	162-180	Alpha-lactalbumin / lysozyme C
91	19-28	Mitochondrial energy transfer proteins
91	143-152	Mitochondrial energy transfer proteins
91	389-398	Mitochondrial energy transfer proteins

FREE TEXT OF SEQUENCE LISTING

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Von Heijne matrix

Score

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oligonucleotide used as a primer

matinspector prediction

name

complement

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Claims

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WHAT IS CLAIMED IS:

1. A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 24-73 or a sequence complementary thereto.
2. A purified or isolated nucleic acid comprising at least 12 consecutive bases of the sequence of one of SEQ ID NOs: 24-73 or one of the sequences complementary thereto.
3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 24-73, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode a mature protein.
5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 24-73 which encode the signal peptide.
6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 74-123.
7. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 74-123.
8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 74-123.
9. A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 74-123.
10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 74-123.
11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 74-123.
12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 74-123.
13. A method of making a protein comprising one of the sequences of SEQ ID NO: 74-123, comprising the steps of:
 - obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 24-73;
 - inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and

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introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA.

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14. The method of Claim 13, further comprising the step of isolating said protein.

15. A protein obtainable by the method of Claim 14.

5 16. A host cell containing a recombinant nucleic acid of Claim 1.

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17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 74-123.

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18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 24-73, or one of the sequences complementary to the sequences of SEQ ID NOs: 24-73, or a fragment thereof of at least 15 consecutive nucleotides.

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19. A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 24-73 or a sequence complementary to one of the sequences of SEQ ID NOs: 24-73.

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15 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 74-123.

21. A computer readable medium having stored thereon a sequence selected from the group consisting of a cDNA code of SEQ ID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123.

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22. A computer system comprising a processor and a data storage device wherein said data storage device has stored thereon a sequence selected from the group consisting of a cDNA code of SEQ ID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123.

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23. The computer system of Claim 22 further comprising a sequence comparer and a data storage device having reference sequences stored thereon.

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24. The computer system of Claim 23 wherein said sequence comparer comprises a computer program which indicates polymorphisms.

25. The computer system of Claim 22 further comprising an identifier which identifies features in said sequence.

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5 26. A method for comparing a first sequence to a reference sequence wherein said first sequence is selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123 comprising the steps of:

10 5 reading said first sequence and said reference sequence through use of a computer program which compares sequences; and
determining differences between said first sequence and said reference sequence with said computer program.

15 27. The method of Claim 26, wherein said step of determining differences between the first sequence and the reference sequence comprises identifying polymorphisms.

20 28. A method for identifying a feature in a sequence selected from the group consisting of a cDNA code of SEQID NOs. 24-73 and a polypeptide code of SEQ ID NOs. 74-123 comprising the steps of:
reading said sequence through the use of a computer program which identifies features in sequences; and
identifying features in said sequence with said computer program.

25 29. A purified or isolated nucleic acid comprising a contiguous span of at least 12 nucleotides of the sequence of one of SEQ ID NOs: 24-73 or one of the sequences complementary thereto, wherein said contiguous span comprises at least 1 of the nucleotide positions of polynucleotides described in Table III.

30 30. A purified or isolated nucleic acid comprising a contiguous span of at least 12 nucleotides of the sequence of one of the polynucleotides described in Table III or one of the sequences complementary thereto.
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Step	Search characteristic		Selection Characteristics			Comments
	Program	Strand	Parameters	Identity (%)	Length (bp)	
miscellaneous	FASTA	both	-	90	15	
tRNA	FASTA	both	-	80	60	
rRNA	BLASTN	both	S=108	80	40	
mtRNA	BLASTN	both	S=108	80	40	
Prokaryotic	BLASTN	both	S=144	90	40	
Fungal	BLASTN	both	S=144	90	40	
Alu	BLASTN	both	S=72, B=5	70	40	max 5 matches, masking
L1	BLASTN	both	S=72, B=5	70	40	max 5 matches, masking
Repeats	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W=6, S=10, E=1000, N=-12	90	10	in the last 100 nucleotides
Polyadenylation signal	-	top	AATAAA allowing 1 mismatch			in the 50 nucleotides preceding the 5' end of the polyA
Vertebrate	BLASTN then FASTA	both	-	90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs	BLAST2N	both	-	90	30	
Geneseq	BLASTN	both	W=8, B=10	90	30	
ORF	BLASTP	top	W=8, B=10	-	-	on ORF proteins, max 10 matches
Proteins	BLASTX	top	E = 0.001	70	30	

Parameters used for each step of cDNA analysis

Figure 1

Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

Figure 2

3/13

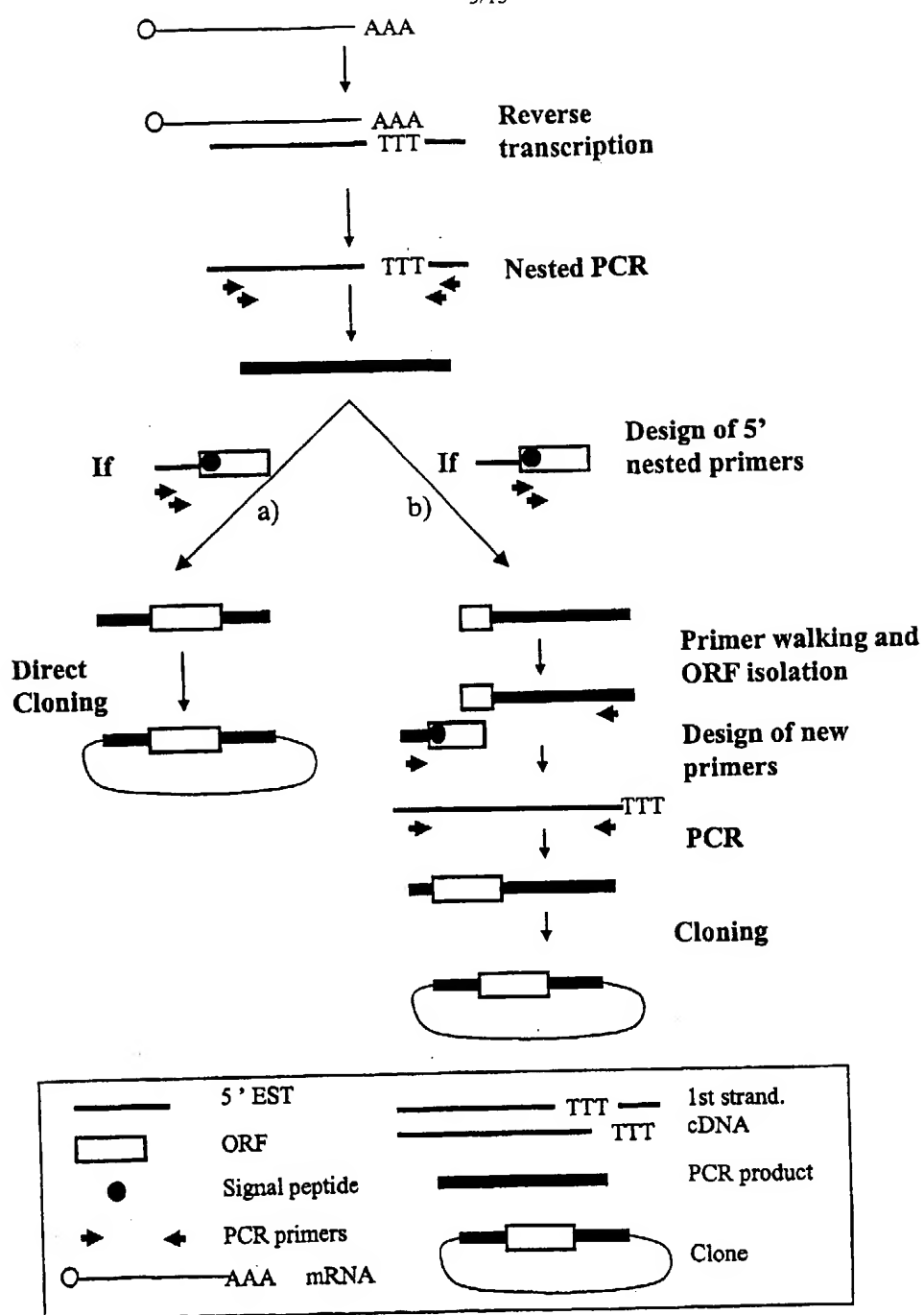


FIGURE 3

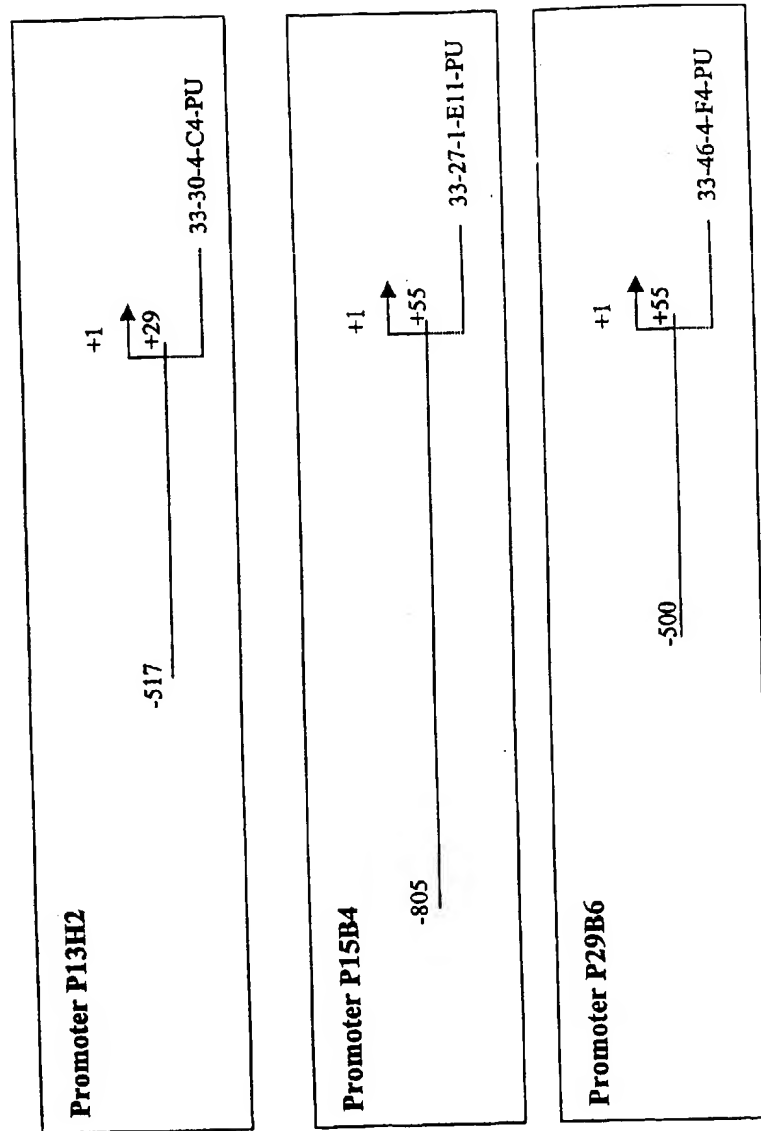


FIGURE 4

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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	-	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	-	0.960	11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHA47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETA47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETA1F2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp) :

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTT
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp) :

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGAAGTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGAAGTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 5

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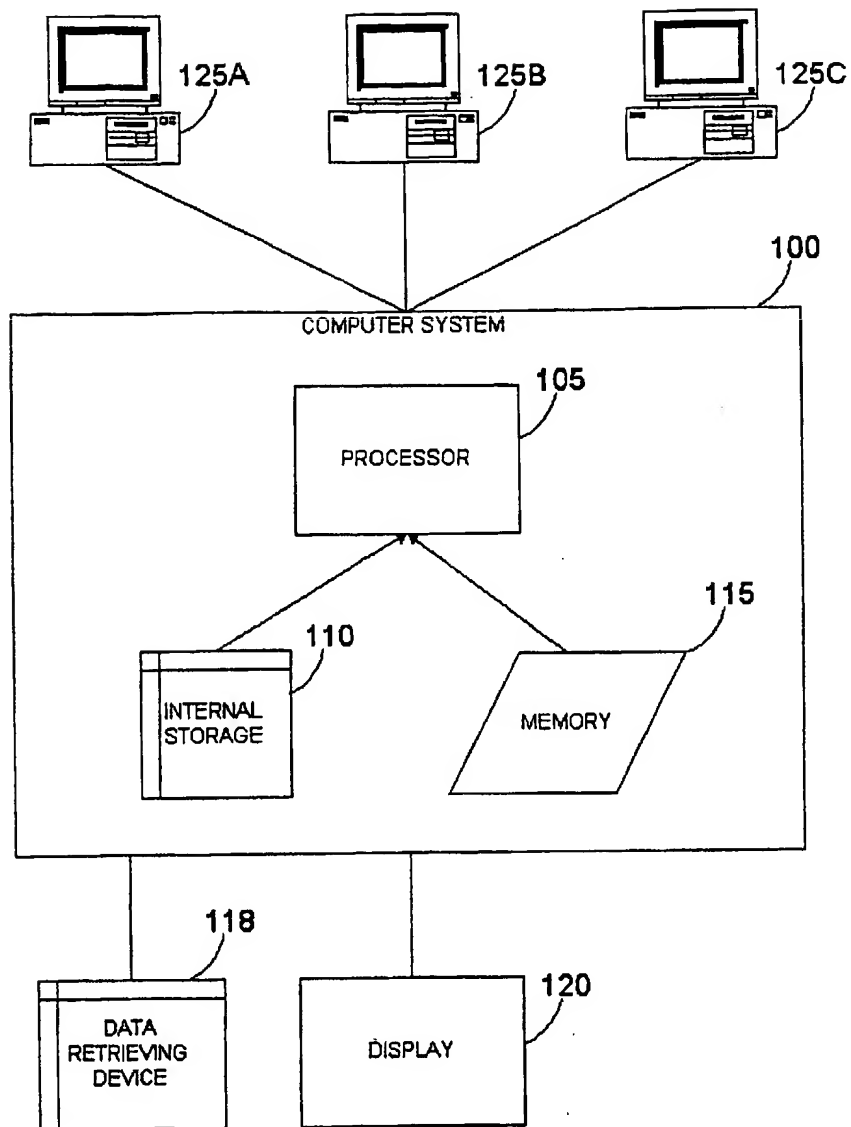


FIGURE 6

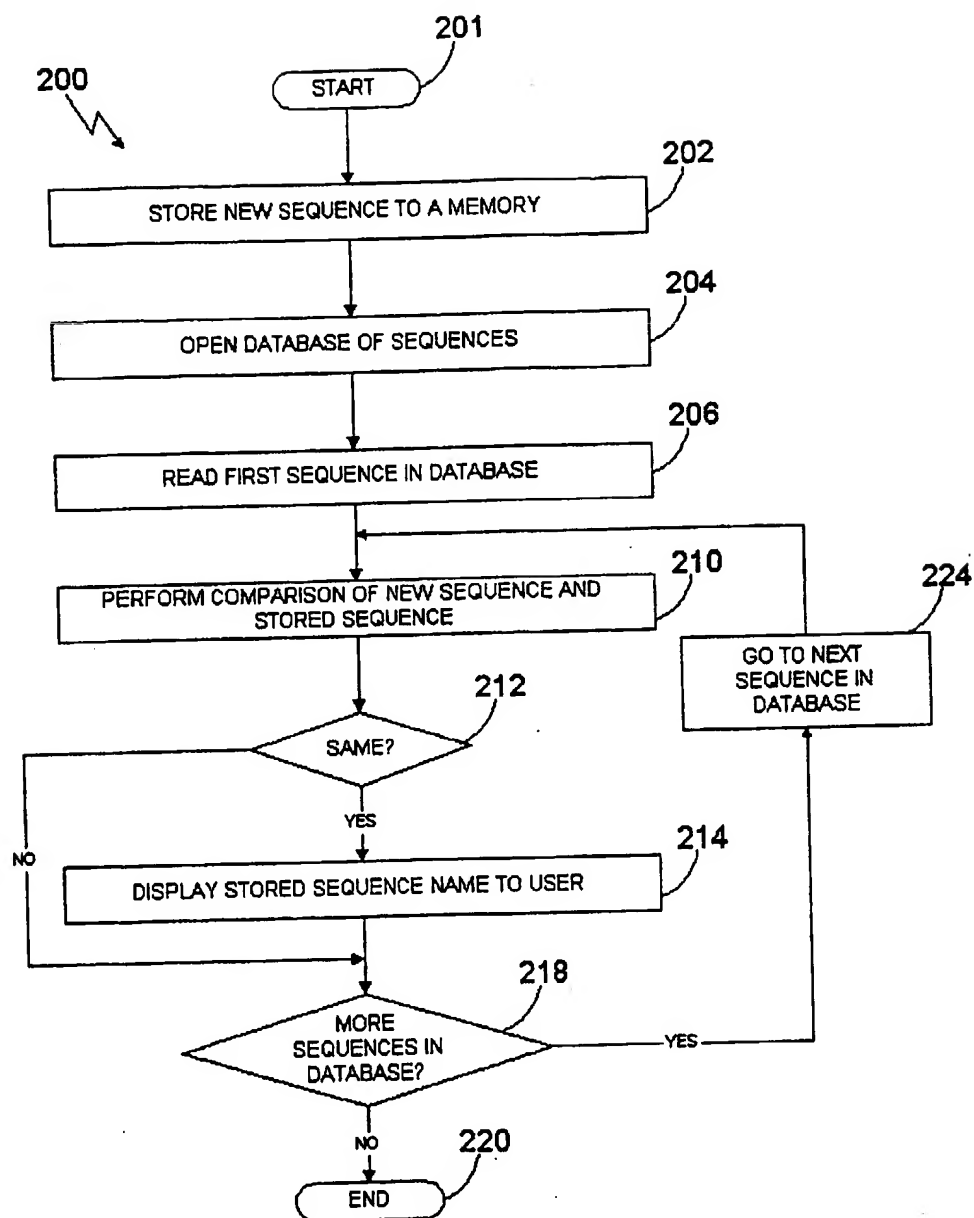


FIGURE 7

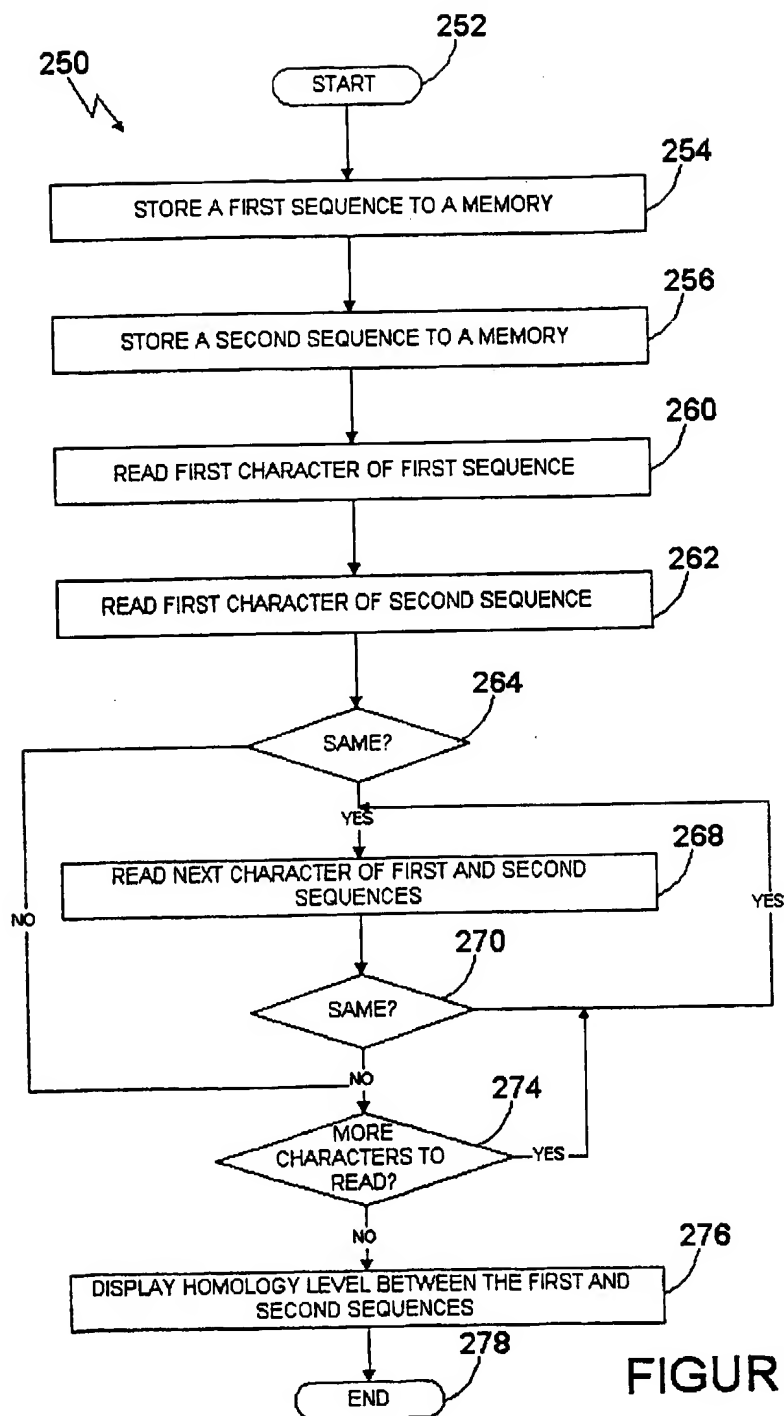


FIGURE 8

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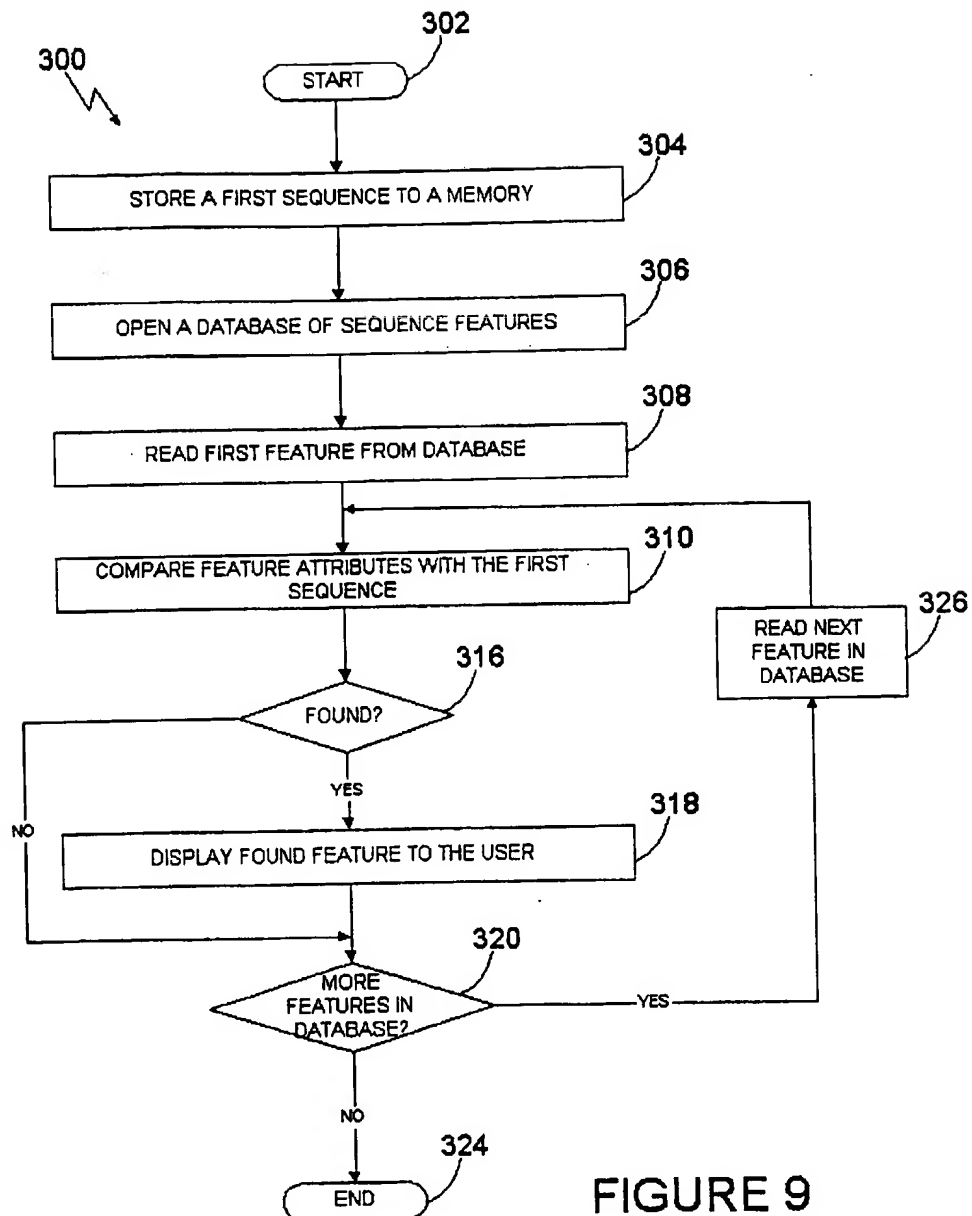


FIGURE 9

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      10      20      30      40      50      60
SEQ ID NO: 76 MLQLWKLVLLCGVLTGTSESLLDNLGNDLSNVVDKLEPVLHEGLETVDNTLKGILEKLV
X:
      10      20      30      40      50      60
SEQ ID NO:124 MLQLWKLVLLCGVLTGTSESLLDNLGNDLSNVVDKLEPVLHEGLETVDNTLKGILEKLV

      70      80      90     100     110     120
SEQ ID NO: 76 DLGVLQKSSAWQLAKQKAQEA EKLLNNVISKLLPTNTDIFGLKISNSLILDVKAEPIDDG
:
      70      80      90     100     110     120
SEQ ID NO:124 DLGVLQKSSAWQLAKQKAQEA EKLLNNVISKLLPTNTDIFGLKISNSLILDVKAEPIDDG

      130     140     150     160     170     180
SEQ ID NO: 76 KGLNLSFPVTANVTAGPIIGQIINLKASDLLTAVTIETDPQTHQPVAVLGE CASDPTS
:
      130     140     150     160     170     180
SEQ ID NO:124 KGLNLSFPVTANVTAGPIIGQIINLKASDLLTAVTIETDPQTHQPVAVLGE CASDPTS

      190     200     210     220     230     240
SEQ ID NO: 76 ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ
:
      190     200     210     220     230     240
SEQ ID NO:124 ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ

SEQ ID NO: 76 HKTQLQTLI
:
SEQ ID NO:124 HKTQLQTLI
```

Figure 10

11/13

```

      10      20      30      40      50      60
SEQ ID NO: 93 MGLLLPLALCILVLCGGAMSPQALNPSALLSRGCNDSVDLAVAGFALRDINKDRKDG
X:.....
SEQ ID NO:125 MGLLLPLALCILVLCGGAMSPQALNPSALLSRGCNDSVDLAVAGFALRDINKDRKDG
      10      20      30      40      50      60

      70      80      90      100     110     120
SEQ ID NO: 93 VLRLNRVNDQYRRGGLGSLFYLTLDVLETDCHVLRKKAWQDCGMRIFFESVYGQCKAI
:.....
SEQ ID NO:125 VLRLNRVNDQYRRGGLGSLFYLTLDVLETDCHVLRKKAWQDCGMRIFFESVYGQCKAI
      70      80      90      100     110     120

      130     140     150     160     170     180
SEQ ID NO: 93 FYMNNPSRVLYLAAYNCTLRPVSKKIYMTCPDCPSSIPTDSSNHQVLEAATESLAKYNN
:.....
SEQ ID NO:125 FYMNNPSRVLYLAAYNCTLRPVSKKIYMTCPDCPSSIPTDSSNHQVLEAATESLAKYNN
      130     140     150     160     170     180

      190     200     210     220     230     240
SEQ ID NO: 93 ENTSKQYSLFKVTRASSQWVVGPSYFVEYLIKESPTKSQASSCSLQSSDSVPVGLCKGS
:.....
SEQ ID NO:125 ENTSKQYSLFKVTRASSQWVVGPSYFVEYLIKESPTKSQASSCSLQSSDSVPVGLCKGS
      190     200     210     220     230     240

      250     260     270     280     290     300
SEQ ID NO: 93 LTRTHWEKFVSVTCDFEFESQAPATGSENSAVNQKPTNLPKVEESQKNTPTDPSKAGP
:.....
SEQ ID NO:125 LTRTHWEKFVSVTCDFEFESQAPATGSENSAVNQKPTNLPKVEESQKNTPTDPSKAGP
      250     260     270     280     290     300

      310     320     330     340     350     360
SEQ ID NO: 93 RGSVQYLPDLDDKNSQEKGPQEAFVHLDLTTPQGETLDSFLFLEPMEEKLVVLPFPK
:.....
SEQ ID NO:125 RGSVQYLPDLDDKNSQEKGPQEAFVHLDLTTPQGETLDSFLFLEPMEEKLVVLPFPK
      310     320     330     340     350     360

      370     380
SEQ ID NO: 93 EKARTAECPGPAQNASPLVLPP
:.....X
SEQ ID NO:125 EKARTAECPGPAQNASPLVLPP
      370     380

```

Figure 11

```

      10      20      30      40      50      60
SEQ ID NO: 75 MKAPGRLVLIILCSVVFSAVYIILLCCWAGLPLCLATCLDHHFPTGSRPTVPGPLHFSGYS
X::::::::::::::::::
SEQ ID NO:126 MKAPGRLLLLTLCILTFSAVCVFLCCWACLPLCLATCLDRHLPAAPRSTVPGPLHFSGYS
      10      20      30      40      50      60

      70      80      90     100     110     120
SEQ ID NO: 75 SVPDGKPLVREPCRSCAVVSSSGQMLGSGGLGAEIDSAECVFRMNQAPTVGFEADVGQRST
::::::::::::::::::
SEQ ID NO:126 SVPDGKPLIRELCHSCAVVSSSGQMLGSGGLGAQIDGAECVLRMNQAPTVGFEEDVGQRST
      70      80      90     100     110     120

      130     140     150     160     170     180
SEQ ID NO: 75 LRVVSHTSVPLLLRNYSHYFQKARDTLYMVWGQGRHMDRVLGGRTYRTLLQLTRMYPGLQ
::::::::::::::::::
SEQ ID NO:126 LRVISHTSVPLLLRNYSHYFQHARDTLYVVWGQGRHMDRVLGGRTYRTLLQLTRMYPGLQ
      130     140     150     160     170     180

      190     200     210     220     230     240
SEQ ID NO: 75 VYTFTERMMAYCDQIFQDETGKNRRQSGSFLSTGWFTMILALELCEEIVVYGMVSDSYCR
::::::::::::::::::
SEQ ID NO:126 VYTFTERMMAYCDQIFQDETGKNRRQSGSFLSTGWFTMILALELCEEIVVYGMVSDSYCS
      190     200     210     220     230     240

      250     260     270     280     290     300
SEQ ID NO: 75 EKSHPSVPYHYFEKGRLDECQMYLAHEQAPRSAHRFITEKAVFSRWAKKRPIVFAHPSWR
::::::::::::::::::X
SEQ ID NO:126 EKSPRSVPYHYFEKGRLDECQMYRLHEQAPRSAHRFITEKAVFSRWAKKRPIVFAHPSWR
      250     260     270     280     290     300

SEQ ID NO: 75 TE
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SEQ ID NO:126 AK

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Figure 12

FIGURE 13

FIGURE 13

<110> Genset

<120> Complementary DNA's Encoding Proteins with Signal Peptides

<130> 56.WO1

<150> 60/113,686

<151> 1998-12-22

<150> 60/141,032

<151> 1999-06-25

<160> 176

<170> Patent.pm

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<223> Von Heijne matrix

score 4.1

seq LPSLAHLLPALDC/LE

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<220>

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<223> n=a, g, c or t

<400> 1

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agaaggggac ccaagggggtc ggccgcggcc aaggcccta ggaccgccgc ccagctcac      120
gctgccagcg gcagctatag acattctgcg tcaggtccgg gctcctggac tttgcctttc      180
ccgagccctg gaggtgggga gaaaagggtc accaattttt aaaatccaaa tatatctcat      240
ggntacagtg gnaagaactg gccagagagt ctggaagntt tgggnttctg gtcctggctg      300
tgccaactgac tcaactgtgac ctgggatct tgtgctgtga agacatttcc caagtgttc      360
atgttagcca gcaaactga cccacanggc ctggaaagag gtgattgtta ggttgcgtag      420
aggtggtctt atccagctca gcttcccctg ggaccaccg tgggacctga ggcagaactg      480
gggtggactt ggctcctcc atg gca cac cgg ctg cag ata cga ctg ctg acg      533
Met Ala His Arg Leu Gln Ile Arg Leu Leu Thr
-240 -235
tgg gat gtg aag gac acg ctg ctc agg ctc cgc cac ccc tta ggg gag      581
Trp Asp Val Lys Asp Thr Leu Leu Arg Leu Arg His Pro Leu Gly Glu
-230 -225 -220
gcc tat gcc acc aag gcc cgg gcc cat ggg ctg gag gtg gag ccc tca      629
Ala Tyr Ala Thr Lys Ala Arg Ala His Gly Leu Glu Val Glu Pro Ser
-215 -210 -205
gcc ctg gaa caa ggc ttc agg cag gca tac agg gct cag agc cac agc      677
Ala Leu Glu Gln Gly Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser
-200 -195 -190 -185
ttc ccc aac tac ggc ctg agc cac ggc cta acc tcc cgc cag tgg tgg      725
Phe Pro Asn Tyr Gly Leu Ser His Gly Leu Thr Ser Arg Gln Trp Trp
-180 -175 -170
ctg gat gtg gtc ctg cag acc ttc cac ctg gcg ggt gtc cag gat gct      773
Leu Asp Val Val Leu Gln Thr Phe His Leu Ala Gly Val Gln Asp Ala
-165 -160 -155
cag gct gta gcc ccc atc gct gaa cag ctt tat aaa gac ttc agc cac      821
Gln Ala Val Ala Pro Ile Ala Glu Gln Leu Tyr Lys Asp Phe Ser His
-150 -145 -140
ccc tgc acc tgg cag gtg ttg gat ggg gct gag gac acc ctg agg gag      869
Pro Cys Thr Trp Gln Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu
-135 -130 -125
tgc cgc aca cgg ggt ctg aga ctg gca gtg atc tcc aac ttt gac cga      917
Cys Arg Thr Arg Gly Leu Arg Leu Ala Val Ile Ser Asn Phe Asp Arg
-120 -115 -110 -105
cgg cta gag ggc atc ctg gag ggc ctt ggc ctg cgt gaa cac ttc gac      965
Arg Leu Glu Gly Ile Leu Glu Gly Leu Gly Leu Arg Glu His Phe Asp

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3

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-100          -95          -90
ttt gtg ctg acc tcc gag gct gct ggc tgg ccc aag ccg gac ccc cgc    1013
Phe Val Leu Thr Ser Glu Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg
-85          -80          -75
att ttc cag gag gcc ttg cgg ctt gct cat atg gaa cca gta gtg gca    1061
Ile Phe Gln Glu Ala Leu Arg Leu Ala His Met Glu Pro Val Val Ala
-70          -65          -60
gcc cat gtt ggg gat aat tac ctc tgc gat tac cag ggg cct cgg gct    1109
Ala His Val Gly Asp Asn Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala
-55          -50          -45
gtg ggc atg cac agc ttc ctg gtg gtt ggc cca cag gca ctg gac ccc    1157
Val Gly Met His Ser Phe Leu Val Val Gly Pro Gln Ala Leu Asp Pro
-40          -35          -30          -25
gtg gtc agg gat tct gta cct aaa gaa cac atc ctc ccc tct ctg gcc    1205
Val Val Arg Asp Ser Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala
-20          -15          -10
cat ctc ctg cct gcc ctt gac tgc cta gag ggc tca act cca ggg ctt    1253
His Leu Leu Pro Ala Leu Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu
-5          1          5
tgaggccagt gaggaagtg gctgggccct aggccatgga gaaaacctta aacaaacctt    1313
ggagacaggg agcccccttct ttctccacag ctctggacct ttccccctct ccttgccggc    1373
tttgtcacct actgtgataa taaagcagtg agtgctgagc tctcaccctt ccccccccaa    1433
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<211> 251

<212> PRT

<213> Homo sapiens

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<221> SIGNAL

<222> -243..-1

<400> 2

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Thr Leu Leu Arg Leu Arg His Pro Leu Gly Glu Ala Tyr Ala Thr Lys
-225          -220          -215
Ala Arg Ala His Gly Leu Glu Val Glu Pro Ser Ala Leu Glu Gln Gly
-210          -205          -200
Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe Pro Asn Tyr Gly
-195          -190          -185          -180

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4

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Leu Ser His Gly Leu Thr Ser Arg Gln Trp Trp Leu Asp Val Val Leu
               -175               -170               -165
Gln Thr Phe His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro
               -160               -155               -150
Ile Ala Glu Gln Leu Tyr Lys Asp Phe Ser His Pro Cys Thr Trp Gln
               -145               -140               -135
Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly
               -130               -125               -120
Leu Arg Leu Ala Val Ile Ser Asn Phe Asp Arg Arg Leu Glu Gly Ile
               -115               -110               -105               -100
Leu Glu Gly Leu Gly Leu Arg Glu His Phe Asp Phe Val Leu Thr Ser
               -95               -90               -85
Glu Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala
               -80               -75               -70
Leu Arg Leu Ala His Met Glu Pro Val Val Ala Ala His Val Gly Asp
               -65               -60               -55
Asn Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala Val Gly Met His Ser
               -50               -45               -40
Phe Leu Val Val Gly Pro Gln Ala Leu Asp Pro Val Val Arg Asp Ser
               -35               -30               -25               -20
Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala His Leu Leu Pro Ala
               -15               -10               -5
Leu Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu
               1               5

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<210> 3

<211> 1448

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<213> Homo sapiens

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<223> Von Heijne matrix

score 5.31

seq AIALATVLFLLIGA/FL

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<221> polyA_site

<222> 1434..1448

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cgctgccaac cgtgggcgag ctctgggtgt gcgggcggcc tcgcgcggcg ctccgctgtg      120
tcagcgtgtt atg atg ccg tcc cgt acc aac ctg gct act gga atc ccc      169
      Met Met Pro Ser Arg Thr Asn Leu Ala Thr Gly Ile Pro
                -55                -50                -45
agt agt aaa gtg aaa tat tca agg ctc tcc agc aca gac gat ggc tac      217
Ser Ser Lys Val Lys Tyr Ser Arg Leu Ser Ser Thr Asp Asp Gly Tyr
                -40                -35                -30
att gac ctt cag ttt aag aaa acc cct cct aag atc cct tat aag gcc      265
Ile Asp Leu Gln Phe Lys Lys Thr Pro Pro Lys Ile Pro Tyr Lys Ala
                -25                -20                -15
atc gca ctt gcc act gtg ctg ttt ttg att ggc gcc ttt ctc att att      313
Ile Ala Leu Ala Thr Val Leu Phe Leu Ile Gly Ala Phe Leu Ile Ile
                -10                -5                1
ata ggc tcc ctc ctg ctg tca ggc tac atc agc aaa ggg ggg gca gac      361
Ile Gly Ser Leu Leu Leu Ser Gly Tyr Ile Ser Lys Gly Gly Ala Asp
5                10                15                20
cgg gcc gtt cca gtg ctg atc att ggc att ctg gtg ttc cta ccc gga      409
Arg Ala Val Pro Val Leu Ile Ile Gly Ile Leu Val Phe Leu Pro Gly
                25                30                35
ttt tac cac ctg cgc atc gct tac tat gca tcc aaa ggc tac cgt ggt      457
Phe Tyr His Leu Arg Ile Ala Tyr Tyr Ala Ser Lys Gly Tyr Arg Gly
                40                45                50
tac tcc tat gat gac att cca gac ttt gat gac tagcaccac cccatagctg      510
Tyr Ser Tyr Asp Asp Ile Pro Asp Phe Asp Asp
                55                60
aggaggagtc acagtggaac tgtcccagct ttaagatatc tagcagaaac tatagctgag      570
gactaaggaa ttctgcagct tgcagatgtt taagaaaata atggccagat tttttgggtc      630
cttcccaaag atgttaagtg aacctacagt tagctaatta ggacaagctc tatttttcat      690
ccctgggccc tgacaagttt ttccacagga atatgtatca tggaagaata gaggttattc      750
tgtaatggaa aagtgttgcc tgccaccacc ctctgtagag ctgagcattt cttttaaata      810
gtcttcattg ccaatttggt cttgtagcaa atggaacaat gtggtatggc taattttotta      870
ttattaagta atttatttta aaaatatctg agtatattat cctgtacact tatccctacc      930
ttcatgttcc agtggagac cttagtaaaa tcaaagatca gtgagttcat ctgtaatatt      990

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ttttttactt gctttcttac tgacagcaac caggaatttt ttatcctgc agagcaagtt 1050
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agtaggttgg acagcatata atttgcacga ttttgtccct tgtaaataca gatgttctgc 1170
agattattcc ttttaacggcc ggaacttttg ctgtttccta atgaaacatg tagtggttat 1230
tatttagagt ttatagccgt attgctagca cctttagta tgatcatcatt ctgctcatga 1290
ttccaaggat cagcctggat gcctagagga ctagatcacc ttagtttgat tctatTTTTT 1350
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<212> PRT

<213> Homo sapiens

<220>

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<400> 4

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Val Lys Tyr Ser Arg Leu Ser Ser Thr Asp Asp Gly Tyr Ile Asp Leu
      -40                -35                -30
Gln Phe Lys Lys Thr Pro Pro Lys Ile Pro Tyr Lys Ala Ile Ala Leu
      -25                -20                -15                -10
Ala Thr Val Leu Phe Leu Ile Gly Ala Phe Leu Ile Ile Ile Gly Ser
              -5                1                5
Leu Leu Leu Ser Gly Tyr Ile Ser Lys Gly Gly Ala Asp Arg Ala Val
      10                15                20
Pro Val Leu Ile Ile Gly Ile Leu Val Phe Leu Pro Gly Phe Tyr His
      25                30                35
Leu Arg Ile Ala Tyr Tyr Ala Ser Lys Gly Tyr Arg Gly Tyr Ser Tyr
      40                45                50                55
Asp Asp Ile Pro Asp Phe Asp Asp
              60

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<210> 5

<211> 1515

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<213> Homo sapiens

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score 7.01

seq LASFAALVLCRQ/RV

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<222> 1500..1515

<400> 5

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gaggaacctg gcacctgcca tctcttcccc caatttgcca ctccagcag ctttagccca      120
tgaggaggat gtgaccggga ctgagtcagg agccctctgg aagc atg gag act gtg      176
                                     Met Glu Thr Val

gtg att gtt gcc ata ggt gtg ctg gcc acc atc ttt ctg gct tcg ttt      224
Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe Leu Ala Ser Phe
-25          -20          -15          -10
gca gcc ttg gtg ctg gtt tgc agg cag cgc tac tgc cgg ccg cga gac      272
Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys Arg Pro Arg Asp
          -5          1          5
ctg ctg cag cgc tat gat tct aag ccc att gtg gac ctc att ggt gcc      320
Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp Leu Ile Gly Ala
          10          15          20
atg gag acc cag tct gag ccc tct gag tta gaa ctg gac gat gtc gtt      368
Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu Asp Asp Val Val
          25          30          35
atc acc aac ccc cac att gag gcc att ctg gag aat gaa gac tgg atc      416
Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn Glu Asp Trp Ile
          40          45          50          55
gaa gat gcc tcg ggt ctc atg tcc cac tgc att gcc atc ttg aag att      464
Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala Ile Leu Lys Ile
          60          65          70
tgt cac act ctg aca gag aag ctt gtt gcc atg aca atg ggc tct ggg      512

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Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr Met Gly Ser Gly
 75 80 85
 gcc aag atg aag act tca gcc agt gtc agc gac atc att gtg gtg gcc 560
 Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile Ile Val Val Ala
 90 95 100
 aag cgg atc agc ccc agg gtg gat gat gtt gtg aag tcg atg tac cct 608
 Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys Ser Met Tyr Pro
 105 110 115
 ccg ttg gac ccc aaa ctc ctg gac gca cgg acg act gcc ctg ctc ctg 656
 Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr Ala Leu Leu Leu
 120 125 130 135
 tct gtc agt cac ctg gtg ctg gtg aca agg aat gcc tgc cat ctg acg 704
 Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala Cys His Leu Thr
 140 145 150
 gga ggc ctg gac tgg att gac cag tct ctg tcg gct gct gag gag cat 752
 Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala Ala Glu Glu His
 155 160 165
 ttg gaa gtc ctt cga gaa gca gcc cta gct tct gag cca gat aaa ggc 800
 Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu Pro Asp Lys Gly
 170 175 180
 ctc cca ggc cct gaa ggc ttc ctg cag gag cag tct gca att 842
 Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser Ala Ile
 185 190 195
 tagtgccctac aggccagcag ctagccatga aggccccctgc cgccatccct ggatggctca 902
 gcttagcctt ctactttttt ctatagagtt agttgttctc cacggctgga gagttcagct 962
 gtgtgtgcat agtaaagcag gagatccccg tcagtattatg cctcttttgc agttgcaaac 1022
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 aggtttgggt ttgaagctga ggaactacaa agttgatgat ttctttttta tctttatgcc 1442
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 aaaaaaaaaaaa aaa 1515

<210> 6

<211> 226

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -29...-1

<400> 6

Met Glu Thr Val Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe
-25 -20 -15
Leu Ala Ser Phe Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys
-10 -5 1
Arg Pro Arg Asp Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp
5 10 15
Leu Ile Gly Ala Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu
20 25 30 35
Asp Asp Val Val Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn
40 45 50
Glu Asp Trp Ile Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala
55 60 65
Ile Leu Lys Ile Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr
70 75 80
Met Gly Ser Gly Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile
85 90 95
Ile Val Val Ala Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys
100 105 110 115
Ser Met Tyr Pro Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr
120 125 130
Ala Leu Leu Leu Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala
135 140 145
Cys His Leu Thr Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala
150 155 160
Ala Glu Glu His Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu
165 170 175
Pro Asp Lys Gly Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser
180 185 190 195
Ala Ile

<210> 7

<211> 1918

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 238..612

<220>
 <221> sig_peptide
 <222> 238..348
 <223> Von Heijne matrix
 score 9.4
 seq LLCCVLSASQLSS/QD

<220>
 <221> polyA_signal
 <222> 1885..1890

<220>
 <221> polyA_site
 <222> 1905..1918

<220>
 <221> misc_feature
 <222> 945,1624
 <223> n=a, g, c or t

<400> 7
 aaaaaatctaa gcgacttcga tgccaaggaa gttgtgtataa tgtgcacgcg ctacaccaca 60
 cccagggtgg aaaccacagt tgcagagtca ttaaacaatc aattgtttgt ttaacatctg 120
 tgataggcag ctttccttct tttcaacagt gatacctacg aaaatcaaaa taaatgcaag 180
 ctgagggtttt gtgctcactg aaagggtctgt caaccccaga aggcgcgacac aaaaaaa 237
 atg gta tgt gaa gat gca ccg tct ttt caa atg gcc tgg gag agt caa 285
 Met Val Cys Glu Asp Ala Pro Ser Phe Gln Met Ala Trp Glu Ser Gln
 -35 -30 -25
 atg gcc tgg gag agg ggg cct gcc ctt ctc tgc tgt gtc ctt tcg gct 333
 Met Ala Trp Glu Arg Gly Pro Ala Leu Leu Cys Cys Val Leu Ser Ala
 -20 -15 -10
 tcc cag ttg agc tcc caa gac cag gac cca ctg ggg cat ata aaa tct 381
 Ser Gln Leu Ser Ser Gln Asp Gln Asp Pro Leu Gly His Ile Lys Ser
 -5 1 5 10
 ctg ctg tat cct ttc ggc ttc cca gtt gag ctc cca aga cca gga ccc 429
 Leu Leu Tyr Pro Phe Gly Phe Pro Val Glu Leu Pro Arg Pro Gly Pro
 15 20 25
 act ggg gca tat aaa aaa gtc aaa aat caa aat caa aca aca agt tct 477
 Thr Gly Ala Tyr Lys Lys Val Lys Asn Gln Asn Gln Thr Thr Ser Ser
 30 35 40
 gag tta ctt agg aaa cag act tcg cat ttc aat cag aga ggc cac aga 525

Glu Leu Leu Arg Lys Gln Thr Ser His Phe Asn Gln Arg Gly His Arg
 45 50 55
 gca agg tct aaa ctt ctg gct tct aga caa att cct gat aga aca ttt 573
 Ala Arg Ser Lys Leu Leu Ala Ser Arg Gln Ile Pro Asp Arg Thr Phe
 60 65 70 75
 aaa tgt ggg aag tgg ctt ccc cag gtc cca tcc cct gtt tagggataga 622
 Lys Cys Gly Lys Trp Leu Pro Gln Val Pro Ser Pro Val
 80 85
 gttgatatca tttttatagt tgccatgtat gcctctgcct gaattttttt aattgacttt 682
 tgagcttttg agattgcacg agggagaaca aggcctttgc tgttgtggat aggaaagact 742
 taacctaaaa ttaaacccagc aagaaagcat tagtaaaaat ctaacaatat gaagggctct 802
 tatgagtcac ttttttcaaa agatgaaaac tccagaaaacg cacaggaacg aaatacctcc 862
 cagaacatcg aagcaatcat cgaagactca ctggtaatat ttttaaaaag tatacagatc 922
 aaagcaaaaa gaagccatgt gtnaacaaaag agaaatgtgc aaatatTTTT taaggcagta 982
 ttaagtgcac gagagtaac atgaaataaa cattctttca catggctact gggaatataa 1042
 atttcgctcc agaaaggccg tagcagtttg acgatagggt gcaaacctt aagatttgtt 1102
 actggggccc agaattttta tttctaggaa tgtatcctga ggaaattatc cgagatcccc 1162
 acaaaactgca atgttttagga attgtcctta tagcattgca tacacaagaa aaacagagaa 1222
 aagcctgac cctgtcagtg gaaaaggggt tcaatgaatt acggtgtgtc tgcattgaggc 1282
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 taacactttg ggaggccaag gtgggaagat tgcctgagct caggagtttg agaccagcct 1402
 gggcaaacacg gtgaaacccc gtctctacta aaatacaaaa aattagccgg gcgtcgagc 1462
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 gattccggtc ccaagaaaaa aaaattgttc aacaataagg gncaaaggga gagaatcata 1642
 acatctgatt aaacagaaaa agcaagattt ttaaaactaa ctatataagg atgggtccag 1702
 ctgtgtcaaa aggaagcttg tttgtaatac gtgtgcataa aaattaaata gaggtgaaca 1762
 caattatttt aaggcagtta aattatctct gtattgtgaa ctaagacttt ctagaatttt 1822
 acttattcat tctgtactta aattttttct aatgaacaca tatacttttg taatcagaaa 1882
 atattaaatg catgtatttt tcaaaaaaaaa aaaaaa 1918

<210> 8

<211> 125

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 8

Met Val Cys Glu Asp Ala Pro Ser Phe Gln Met Ala Trp Glu Ser Gln

12

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      -35      -30      -25
Met Ala Trp Glu Arg Gly Pro Ala Leu Leu Cys Cys Val Leu Ser Ala
      -20      -15      -10
Ser Gln Leu Ser Ser Gln Asp Gln Asp Pro Leu Gly His Ile Lys Ser
      -5      1      5      10
Leu Leu Tyr Pro Phe Gly Phe Pro Val Glu Leu Pro Arg Pro Gly Pro
      15      20      25
Thr Gly Ala Tyr Lys Lys Val Lys Asn Gln Asn Gln Thr Thr Ser Ser
      30      35      40
Glu Leu Leu Arg Lys Gln Thr Ser His Phe Asn Gln Arg Gly His Arg
      45      50      55
Ala Arg Ser Lys Leu Leu Ala Ser Arg Gln Ile Pro Asp Arg Thr Phe
      60      65      70      75
Lys Cys Gly Lys Trp Leu Pro Gln Val Pro Ser Pro Val
      80      85

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<210> 9

<211> 852

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 229..735

<220>

<221> sig_peptide

<222> 229..492

<223> Von Heijne matrix

score 6.7

seq VFALSSFLNKASA/VY

<220>

<221> polyA_signal

<222> 816..821

<220>

<221> polyA_site

<222> 841..852

<400> 9

aatgactggc agtggcatca gcgatggcgg ctgcgtcggg gtcggttctg cagcgtctga

60

tcgtgtcgcc ggcagggagg catagcgcc cctgatctt cctgcatggc tcaggtgatt 120
 ctggacaagg attaagaatg tggatcaagc aggtttttta atcaagattt aacattccaa 180
 cacataaaaa ttatttatcc aacagctcct cccagatcat atactcct atg aaa gga 237
 Met Lys Gly
 gga atc tcc aat gta tgg ttt gac aga ttt aaa ata acc aat gac tgc 285
 Gly Ile Ser Asn Val Trp Phe Asp Arg Phe Lys Ile Thr Asn Asp Cys
 -85 -80 -75 -70
 cca gaa cac ctt gaa tca att gat gtc atg tgt caa gtg ctt act gat 333
 Pro Glu His Leu Glu Ser Ile Asp Val Met Cys Gln Val Leu Thr Asp
 -65 -60 -55
 ttg att gat gaa gaa gta aaa agt ggc atc aag aag aac agg ata tta 381
 Leu Ile Asp Glu Glu Val Lys Ser Gly Ile Lys Lys Asn Arg Ile Leu
 -50 -45 -40
 ata gga gga ttc tct atg gga gga tgc atg gca atg cat tta gca tat 429
 Ile Gly Gly Phe Ser Met Gly Gly Cys Met Ala Met His Leu Ala Tyr
 -35 -30 -25
 aga aat cat caa gat gtg gca gga gta ttt gct ctt tct agt ttt ctg 477
 Arg Asn His Gln Asp Val Ala Gly Val Phe Ala Leu Ser Ser Phe Leu
 -20 -15 -10
 aat aaa gca tct gct gtt tac cag gct ctt cag aag agt aat ggt gta 525
 Asn Lys Ala Ser Ala Val Tyr Gln Ala Leu Gln Lys Ser Asn Gly Val
 -5 1 5 10
 ctt cct gaa tta ttt cag tgt cat ggt act gca gat gag tta gtt ctt 573
 Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu Leu Val Leu
 15 20 25
 cat tct tgg gca gaa gag aca aac tca atg tta aaa tct cta gga gtg 621
 His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser Leu Gly Val
 30 35 40
 acc acg aag ttt cat agt ttt cca aat gtt tac cat gag cta agc aaa 669
 Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu Leu Ser Lys
 45 50 55
 act gag tta gac ata ttg aag tta tgg att ctt aca aag ctg cca gga 717
 Thr Glu Leu Asp Ile Leu Lys Leu Trp Ile Leu Thr Lys Leu Pro Gly
 60 65 70 75
 gaa atg gaa aaa caa aaa tgaatgaatc aagagtgatt tgtaaatgta 765
 Glu Met Glu Lys Gln Lys
 80
 agtgtaatgt ctttgtgaaa agtgattttt actgccaaat tataatgata attaaaaatat 825
 taagaaatag caaaaaaaaa aaaaaaa 852

<210> 10

<211> 169

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -88...-1

<400> 10

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Met Lys Gly Gly Ile Ser Asn Val Trp Phe Asp Arg Phe Lys Ile Thr
      -85                      -80                      -75
Asn Asp Cys Pro Glu His Leu Glu Ser Ile Asp Val Met Cys Gln Val
      -70                      -65                      -60
Leu Thr Asp Leu Ile Asp Glu Glu Val Lys Ser Gly Ile Lys Lys Asn
      -55                      -50                      -45
Arg Ile Leu Ile Gly Gly Phe Ser Met Gly Gly Cys Met Ala Met His
      -40                      -35                      -30                      -25
Leu Ala Tyr Arg Asn His Gln Asp Val Ala Gly Val Phe Ala Leu Ser
      -20                      -15                      -10
Ser Phe Leu Asn Lys Ala Ser Ala Val Tyr Gln Ala Leu Gln Lys Ser
      -5                      1                      5
Asn Gly Val Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu
      10                      15                      20
Leu Val Leu His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser
      25                      30                      35                      40
Leu Gly Val Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu
      45                      50                      55
Leu Ser Lys Thr Glu Leu Asp Ile Leu Lys Leu Trp Ile Leu Thr Lys
      60                      65                      70
Leu Pro Gly Glu Met Glu Lys Gln Lys
      75                      80

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<210> 11

<211> 1602

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 24...1004

<220>

<221> sig_peptide

<222> 24..170

<223> Von Heijne matrix

score 5.6

seq ACLSLGFFSLLWL/QL

<220>

<221> polyA_site

<222> 1586..1602

<400> 11

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atgcgccgcc gcctctccgc acg atg ttc ccc tcg cgg agg aaa gcg gcg cag      53
                               Met Phe Pro Ser Arg Arg Lys Ala Ala Gln
                               -45                               -40

ctg ccc tgg gag gac ggc agg tcc ggg ttg ctc tcc ggc ggc ctc cct      101
Leu Pro Trp Glu Asp Gly Arg Ser Gly Leu Leu Ser Gly Gly Leu Pro
                               -35                               -30                               -25

cgg aag tgt tcc gtc ttc cac ctg ttc gtg gcc tgc ctc tcg ctg ggc      149
Arg Lys Cys Ser Val Phe His Leu Phe Val Ala Cys Leu Ser Leu Gly
                               -20                               -15                               -10

ttc ttc tcc cta ctc tgg ctg cag ctc agc tgc tct ggg gac gtg gcc      197
Phe Phe Ser Leu Leu Trp Leu Gln Leu Ser Cys Ser Gly Asp Val Ala
                               -5                               1                               5

cgg gca gtc agg gga caa ggg cag gag acc tcg ggc cct ccc cgt gcc      245
Arg Ala Val Arg Gly Gln Gly Gln Glu Thr Ser Gly Pro Pro Arg Ala
10                               15                               20                               25

tgc ccc cca gag ccg ccc cct gag cac tgg gaa gaa gac gca tcc tgg      293
Cys Pro Pro Glu Pro Pro Pro Glu His Trp Glu Glu Asp Ala Ser Trp
                               30                               35                               40

ggc ccc cac cgc ctg gca gtg ctg gtg ccc ttc cgc gaa cgc ttc gag      341
Gly Pro His Arg Leu Ala Val Leu Val Pro Phe Arg Glu Arg Phe Glu
                               45                               50                               55

gag ctc ctg gtc ttc gtg ccc cac atg cgc cgc ttc ctg agc agg aag      389
Glu Leu Leu Val Phe Val Pro His Met Arg Arg Phe Leu Ser Arg Lys
                               60                               65                               70

aag atc cgg cac cac atc tac gtg ctc aac cag gtg gac cac ttc agg      437
Lys Ile Arg His His Ile Tyr Val Leu Asn Gln Val Asp His Phe Arg
75                               80                               85

ttc aac cgg gca gcg ctc atc aac gtg ggc ttc ctg gag agc agc aac      485
Phe Asn Arg Ala Ala Leu Ile Asn Val Gly Phe Leu Glu Ser Ser Asn
90                               95                               100                               105

agc acg gac tac att gcc atg cac gac gtt gac ctg ctc cct ctc aac      533
Ser Thr Asp Tyr Ile Ala Met His Asp Val Asp Leu Leu Pro Leu Asn

```

16

110	115	120	
gag gag ctg gac tat ggc ttt cct gag gct ggg ccc ttc cac gtg gcc			581
Glu Glu Leu Asp Tyr Gly Phe Pro Glu Ala Gly Pro Phe His Val Ala			
125	130	135	
tcc ccg gag ctg cac cct ctg tac cac tac aag acc tat gtc ggc ggc			629
Ser Pro Glu Leu His Pro Leu Tyr His Tyr Lys Thr Tyr Val Gly Gly			
140	145	150	
atc ctg ctg ctg tcc aag cag cac tac cgg ctg tgc aat ggg atg tcc			677
Ile Leu Leu Leu Ser Lys Gln His Tyr Arg Leu Cys Asn Gly Met Ser			
155	160	165	
aac cgc ttc tgg ggc tgg ggc cgc gag gac gac gag ttc tac cgg cgc			725
Asn Arg Phe Trp Gly Trp Gly Arg Glu Asp Asp Glu Phe Tyr Arg Arg			
170	175	180	185
att aag gga gct ggg ctg cag ctt ttc cgc ccc tgc gga atc aca act			773
Ile Lys Gly Ala Gly Leu Gln Leu Phe Arg Pro Ser Gly Ile Thr Thr			
190	195	200	
ggg tac aag aca ttt cgc cac ctg cat gac cca gcc tgg cgg aag agg			821
Gly Tyr Lys Thr Phe Arg His Leu His Asp Pro Ala Trp Arg Lys Arg			
205	210	215	
gac cag aag cgc atc gca gct caa aaa cag gag cag ttc aag gtg gac			869
Asp Gln Lys Arg Ile Ala Ala Gln Lys Gln Glu Gln Phe Lys Val Asp			
220	225	230	
agg gag gga ggc ctg aac act gtg aag tac cat gtg gct tcc cgc act			917
Arg Glu Gly Gly Leu Asn Thr Val Lys Tyr His Val Ala Ser Arg Thr			
235	240	245	
gcc ctg tct gtg ggc ggg gcc ccc tgc act gtc ctg aac atc atg ttg			965
Ala Leu Ser Val Gly Gly Ala Pro Cys Thr Val Leu Asn Ile Met Leu			
250	255	260	265
gac tgt gac aag acc gcc aca ccc tgg tgc aca ttc agc tgagctggat			1014
Asp Cys Asp Lys Thr Ala Thr Pro Trp Cys Thr Phe Ser			
270	275		
ggacagtgag gaagcctgta cctacaggcc atattgctca ggctcaggac aaggcctcag			1074
gtcgtggggc cagctctgac aggatgtgga gtggccagga ccaagacagc aagctacgca			1134
attgcagcca cccggccgcc aaggcaggct tgggctgggc caggacacgt ggggtgcctg			1194
ggacgtgct tgccatgcac agtgatcaga gagaggctgg ggtgtgtcct gtccgggacc			1254
ccccctgcct tctgtctcac cctactctga cctccttcac gtgccaggc ctgtgggtag			1314
tggggagggc tgaacaggac aacctctcat caccctcact ttgttctctt cctgctgggc			1374
tgccctgtgc agagacacag ttagggggcc atgcagctgg cgtagggtggc agttgggcct			1434
ggtgagggtt aggacttcag aaaccagagc acaagcccca cagaggggga acagccagca			1494
ccgctctagc tggttgttgc catgccgaa tgtgggccta gtgttccag atcttctgat			1554
ttttcgaaag aaactagaat gctggattct caaaaaaaaa aaaaaaaaa			1602

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<220>
<221> SIGNAL
<222> -49..-1
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<400> 12
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      -45                      -40                      -35
Arg Ser Gly Leu Leu Ser Gly Gly Leu Pro Arg Lys Cys Ser Val Phe
      -30                      -25                      -20
His Leu Phe Val Ala Cys Leu Ser Leu Gly Phe Phe Ser Leu Leu Trp
      -15                      -10                      -5
Leu Gln Leu Ser Cys Ser Gly Asp Val Ala Arg Ala Val Arg Gly Gln
      1                      5                      10                      15
Gly Gln Glu Thr Ser Gly Pro Pro Arg Ala Cys Pro Pro Glu Pro Pro
      20                      25                      30
Pro Glu His Trp Glu Glu Asp Ala Ser Trp Gly Pro His Arg Leu Ala
      35                      40                      45
Val Leu Val Pro Phe Arg Glu Arg Phe Glu Glu Leu Leu Val Phe Val
      50                      55                      60
Pro His Met Arg Arg Phe Leu Ser Arg Lys Lys Ile Arg His His Ile
      65                      70                      75
Tyr Val Leu Asn Gln Val Asp His Phe Arg Phe Asn Arg Ala Ala Leu
      80                      85                      90                      95
Ile Asn Val Gly Phe Leu Glu Ser Ser Asn Ser Thr Asp Tyr Ile Ala
      100                      105                      110
Met His Asp Val Asp Leu Leu Pro Leu Asn Glu Glu Leu Asp Tyr Gly
      115                      120                      125
Phe Pro Glu Ala Gly Pro Phe His Val Ala Ser Pro Glu Leu His Pro
      130                      135                      140
Leu Tyr His Tyr Lys Thr Tyr Val Gly Gly Ile Leu Leu Leu Ser Lys
      145                      150                      155
Gln His Tyr Arg Leu Cys Asn Gly Met Ser Asn Arg Phe Trp Gly Trp
      160                      165                      170                      175
Gly Arg Glu Asp Asp Glu Phe Tyr Arg Arg Ile Lys Gly Ala Gly Leu
      180                      185                      190
Gln Leu Phe Arg Pro Ser Gly Ile Thr Thr Gly Tyr Lys Thr Phe Arg
      195                      200                      205

```

18

His Leu His Asp Pro Ala Trp Arg Lys Arg Asp Gln Lys Arg Ile Ala
 210 215 220
 Ala Gln Lys Gln Glu Gln Phe Lys Val Asp Arg Glu Gly Gly Leu Asn
 225 230 235
 Thr Val Lys Tyr His Val Ala Ser Arg Thr Ala Leu Ser Val Gly Gly
 240 245 250 255
 Ala Pro Cys Thr Val Leu Asn Ile Met Leu Asp Cys Asp Lys Thr Ala
 260 265 270
 Thr Pro Trp Cys Thr Phe Ser
 275

<210> 13

<211> 948

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 80..784

<220>

<221> sig_peptide

<222> 80..139

<223> Von Heijne matrix

score 4

seq LLKVVFVVFASLC/AW

<220>

<221> polyA_signal

<222> 910..915

<220>

<221> polyA_site

<222> 933..948

<400> 13

cttcctgacc caggggctcc gctggctgcg gtcgcctggg agctgccgcc agggccagga 60
 ggggagcggc acctggaag atg cgc cca ttg gct ggt ggc ctg ctc aag gtg 112
 Met Arg Pro Leu Ala Gly Gly Leu Leu Lys Val
 -20 -15 -10
 gtg ttc gtg gtc ttc gcc tcc ttg tgt gcc tgg tat tcg ggg tac ctg 160
 Val Phe Val Val Phe Ala Ser Leu Cys Ala Trp Tyr Ser Gly Tyr Leu

19

-5	1	5	
ctc gca gag ctc att cca gat gca ccc ctg tcc agt gct gcc tat agc			208
Leu Ala Glu Leu Ile Pro Asp Ala Pro Leu Ser Ser Ala Ala Tyr Ser			
10	15	20	
atc cgc agc atc ggg gag agg cct gtc ctc aaa gct cca gtc ccc aaa			256
Ile Arg Ser Ile Gly Glu Arg Pro Val Leu Lys Ala Pro Val Pro Lys			
25	30	35	
agg caa aaa tgt gac cac tgg act ccc tgc cca tct gac acc tat gcc			304
Arg Gln Lys Cys Asp His Trp Thr Pro Cys Pro Ser Asp Thr Tyr Ala			
40	45	50	55
tac agg tta ctc agc gga ggt ggc aga agc aag tac gcc aaa atc tgc			352
Tyr Arg Leu Leu Ser Gly Gly Gly Arg Ser Lys Tyr Ala Lys Ile Cys			
60	65	70	
ttt gag gat aac cta ctt atg gga gaa cag ctg gga aat gtt gcc aga			400
Phe Glu Asp Asn Leu Leu Met Gly Glu Gln Leu Gly Asn Val Ala Arg			
75	80	85	
gga ata aac att gcc att gtc aac tat gta act ggg aat gtg aca gca			448
Gly Ile Asn Ile Ala Ile Val Asn Tyr Val Thr Gly Asn Val Thr Ala			
90	95	100	
aca cga tgt ttt gat atg tat gaa ggc gat aac tct gga ccg atg aca			496
Thr Arg Cys Phe Asp Met Tyr Glu Gly Asp Asn Ser Gly Pro Met Thr			
105	110	115	
aag ttt att cag agt gct gct cca aaa tcc ctg ctc ttc atg gtg acc			544
Lys Phe Ile Gln Ser Ala Ala Pro Lys Ser Leu Leu Phe Met Val Thr			
120	125	130	135
tat gac gac gga agc aca aga ctg aat aac gat gcc aag aat gcc ata			592
Tyr Asp Asp Gly Ser Thr Arg Leu Asn Asn Asp Ala Lys Asn Ala Ile			
140	145	150	
gaa gca ctt gga agt aaa gaa atc agg aac atg aaa ttc agg tct agc			640
Glu Ala Leu Gly Ser Lys Glu Ile Arg Asn Met Lys Phe Arg Ser Ser			
155	160	165	
tgg gta ttt att gca gca aaa ggc ttg gaa ctc cct tcc gaa att cag			688
Trp Val Phe Ile Ala Ala Lys Gly Leu Glu Leu Pro Ser Glu Ile Gln			
170	175	180	
aga gaa aag atc aac cac tct gat gct aag aac aac aga tat tct ggc			736
Arg Glu Lys Ile Asn His Ser Asp Ala Lys Asn Asn Arg Tyr Ser Gly			
185	190	195	
tgg cct gca gag atc cag ata gaa ggc tgc ata ccc aaa gaa cga agc			784
Trp Pro Ala Glu Ile Gln Ile Glu Gly Cys Ile Pro Lys Glu Arg Ser			
200	205	210	215
tgacactgca gggctcctgag taaatgtgtt ctgtataaac aaatgcagct ggaatcgctc			844
aagaatctta ttttttctaaa tccaacagcc catatttgat gagtattttg gggtttgtgt			904

aaaccaatga acatttgcta gttgtaccaa aaaaaaaaaa aaaa

948

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<211> 235

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

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<400> 14

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 Ala Ser Leu Cys Ala Trp Tyr Ser Gly Tyr Leu Leu Ala Glu Leu Ile
 1 5 10
 Pro Asp Ala Pro Leu Ser Ser Ala Ala Tyr Ser Ile Arg Ser Ile Gly
 15 20 25
 Glu Arg Pro Val Leu Lys Ala Pro Val Pro Lys Arg Gln Lys Cys Asp
 30 35 40
 His Trp Thr Pro Cys Pro Ser Asp Thr Tyr Ala Tyr Arg Leu Leu Ser
 45 50 55 60
 Gly Gly Gly Arg Ser Lys Tyr Ala Lys Ile Cys Phe Glu Asp Asn Leu
 65 70 75
 Leu Met Gly Glu Gln Leu Gly Asn Val Ala Arg Gly Ile Asn Ile Ala
 80 85 90
 Ile Val Asn Tyr Val Thr Gly Asn Val Thr Ala Thr Arg Cys Phe Asp
 95 100 105
 Met Tyr Glu Gly Asp Asn Ser Gly Pro Met Thr Lys Phe Ile Gln Ser
 110 115 120
 Ala Ala Pro Lys Ser Leu Leu Phe Met Val Thr Tyr Asp Asp Gly Ser
 125 130 135 140
 Thr Arg Leu Asn Asn Asp Ala Lys Asn Ala Ile Glu Ala Leu Gly Ser
 145 150 155
 Lys Glu Ile Arg Asn Met Lys Phe Arg Ser Ser Trp Val Phe Ile Ala
 160 165 170
 Ala Lys Gly Leu Glu Leu Pro Ser Glu Ile Gln Arg Glu Lys Ile Asn
 175 180 185
 His Ser Asp Ala Lys Asn Asn Arg Tyr Ser Gly Trp Pro Ala Glu Ile
 190 195 200
 Gln Ile Glu Gly Cys Ile Pro Lys Glu Arg Ser
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gggaagatgg agatagtatt gcctg 25

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<220>
<223> oligonucleotide used as a primer

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ctgccatgta catgatagag agattc 26

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score 0.983

sequence tgtcagttg

<220>

<221> protein_bind

<222> complement(18..27)

<223> matinspector prediction

name MYOD_Q6

score 0.961

sequence cccaactgac

<220>

<221> protein_bind

<222> complement(75..85)

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name S8_01

score 0.960

sequence aatagaattag

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name S8_01

score 0.966

sequence aactaaattag

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<222> complement(129..139)

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name DELTAEF1_01

score 0.960

sequence gcacacctcag

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name GATA_C

score 0.964

sequence agataaatcca

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 score 0.958
 sequence cttcagttg

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<222> 176..189
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 name GATA1_02
 score 0.959
 sequence ttgtagataggaca

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 score 0.953
 sequence agataggacat

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 score 0.973
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 score 0.983
 sequence cataacagatggtaag

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<222> 284..299
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score 0.978
sequence cataacagatggtaag

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<222> complement(287..296)
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score 0.954
sequence accatctgtt

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<222> complement(302..314)
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score 0.953
sequence tcaagataaaagta

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name IK1_01
score 0.963
sequence agttgggaattcc

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name IK2_01
score 0.985
sequence agttgggaattc

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<222> 396..405
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name CREL_01
score 0.962
sequence tgggaattcc

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<222> 423..436

<223> matinspector prediction

name GATA1_02

score 0.950

sequence tcagtgatatggca

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<222> complement(478..489)

<223> matinspector prediction

name SRY_02

score 0.951

sequence taaaacaaaaca

<220>

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<222> 486..493

<223> matinspector prediction

name E2F_02

score 0.957

sequence tttagcgc

<220>

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score 0.975

sequence tgagggga

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gttattgact gaggtgtgct aatctcccat tatgtggatt tatctatttc ttcagttgta	180
gataggacat tgatagatac ataagtacca ggacaaaagc agggagatct tttttccaaa	240
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atactttatc ttgagtagga gagccttcct gtggcaacgt ggagaagga agaggtcgta	360
gaattgagga gtcagctcag ttagaagcag ggagttggga attccgttca tgtgatttag	420
catcagtgat atggcaaatg tgggactaag ggtagtgatc agaggggttaa aattgtgtgt	480
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cttcat	546

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<400> 18

gtaccagga ctgtgaccat tgc 23

<210> 19

<211> 24

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<223> oligonucleotide used as a primer

<400> 19

ctgtgaccat tgctccaag agag 24

<210> 20

<211> 861

<212> DNA

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 score 0.962
 sequence cctgggga

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 score 0.994
 sequence tgaccgttg

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 name STAT_01
 score 0.968
 sequence ttcttgga

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score 0.951
sequence ttccaggaa

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name MZF1_01
score 0.956
sequence ttggggga

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score 0.965
sequence gaatgggatttc

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score 0.986
sequence agagggga

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score 0.955
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name MZF1_01

score 0.960
sequence gaagggga

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score 0.981
sequence agcatctgcc

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score 0.958
sequence tcccaccttcc

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name S8_01
score 0.992
sequence gaggcaattat

<220>
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name MZF1_01
score 0.986
sequence agagggga

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30

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cggtgaccgt tggattcctg gaagcagtag ctgttctgtt tggatctggt agggacaggg 180
ctcagagggc taggcacgag ggaaggcag aggagaaggs aggsarggcc cagtgagarg 240
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tctcttggga gcaatggtca c 861

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<213> Artificial Sequence

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<223> oligonucleotide used as a primer

<400> 21

ctgggatgga aggcacggta

20

<210> 22

<211> 20

<212> DNA

<213> Artificial Sequence

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<223> oligonucleotide used as a primer

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gagaccacac agctagacaa

20

<210> 23

<211> 555

<212> DNA

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<222> 501

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 score 0.964
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 name NMYC_01
 score 0.965
 sequence actcacgtgctg

<220>
<221> protein_bind
<222> 193..204
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 name USF_01
 score 0.985
 sequence actcacgtgctg

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 name USF_01
 score 0.985
 sequence cagcacgtgagt

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name NMYC_01
score 0.956
sequence cagcacgtgagt

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name MYCMAX_02
score 0.972
sequence cagcacgtgagt

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name USF_C
score 0.997
sequence tcacgtgc

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name USF_C
score 0.991
sequence gcacgtga

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score 0.968
sequence catgggga

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<222> 397..410
<223> matinspector prediction

name ELK1_02
score 0.963
sequence ctctccggaagcct

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<221> protein_bind

<222> 400..409

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name CETS1P54_01

score 0.974

sequence tccggaagcc

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<222> complement(460..470)

<223> matinspector prediction

name AP1_Q4

score 0.963

sequence agtgactgaac

<220>

<221> protein_bind

<222> complement(460..470)

<223> matinspector prediction

name AP1FJ_Q2

score 0.961

sequence agtgactgaac

<220>

<221> protein_bind

<222> 547..555

<223> matinspector prediction

name PADS_C

score 1.000

sequence tgtggtctc

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kawaagctca	gcaccggtgc	ccatcacagg	gccggcagca	cacacatccc	attactcaga	180
aggaactgac	ggactcacgt	gctgctccgt	ccccatgagc	tcaaggagcc	tgtctatgta	240
gagcagtcag	acagtgctcg	ggatagagtg	agagttcagc	cagtaaatcc	aagtgattgt	300

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cattcctgtc tgcattagta actcccaacc tagatgtgaa aacttagttc tttctcatag 360
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cgtgtcttct gctgtctccc gctcacatcc cacacttggtg ttcagtcact gagttacaga 480
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<211> 1450

<212> DNA

<213> Homo Sapiens

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<221> CDS

<222> 153..1127

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<222> 153..230

<223> Von Heijne matrix

score 8.40

seq RLLRLLLSGLVLG/AA

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<221> polyA_signal

<222> 1415..1420

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<221> polyA_site

<222> 1434..1450

<220>

<221> misc_feature

<222> 88

<223> n=a, g, c or t

<400> 24

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gtgccatgct gcccggcgg cggcgtgaa gg atg gcg acg ccg ctg cct ccg 173
Met Ala Thr Pro Leu Pro Pro
-25 -20
ccc tcc ccg cgg cac ctg cgg ctg ctg cgg ctg ctg etc tcc gcc etc 221

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Pro	Ser	Pro	Arg	His	Leu	Arg	Leu	Leu	Arg	Leu	Leu	Leu	Ser	Gly	Leu	
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Val	Leu	Gly	Ala	Ala	Leu	Arg	Gly	Ala	Ala	Ala	Gly	His	Pro	Asp	Val	
		1					5					10				
gcc	gcc	tgt	ccc	ggg	agc	ctg	gac	tgt	gcc	ctg	aag	agg	cgg	gca	agg	317
Ala	Ala	Cys	Pro	Gly	Ser	Leu	Asp	Cys	Ala	Leu	Lys	Arg	Arg	Ala	Arg	
		15				20					25					
tgt	cct	cct	ggc	gca	cat	gcc	tgt	ggg	ccc	tgc	ctt	cag	ccc	ttc	cag	365
Cys	Pro	Pro	Gly	Ala	His	Ala	Cys	Gly	Pro	Cys	Leu	Gln	Pro	Phe	Gln	
30					35					40				45		
gag	gac	cag	caa	ggg	ctc	tgt	gtg	ccc	agg	atg	cgc	cgg	cct	cca	ggc	413
Glu	Asp	Gln	Gln	Gly	Leu	Cys	Val	Pro	Arg	Met	Arg	Arg	Pro	Pro	Gly	
				50					55				60			
ggg	ggc	cgg	ccc	cag	ccc	aga	ctg	gaa	gat	gag	att	gac	ttc	ctg	gcc	461
Gly	Gly	Arg	Pro	Gln	Pro	Arg	Leu	Glu	Asp	Glu	Ile	Asp	Phe	Leu	Ala	
			65					70				75				
cag	gag	ctt	gcc	cgg	aag	gag	tct	gga	cac	tca	act	ccg	ccc	cta	ccc	509
Gln	Glu	Leu	Ala	Arg	Lys	Glu	Ser	Gly	His	Ser	Thr	Pro	Pro	Leu	Pro	
	80					85					90					
aag	gac	cga	cag	cgg	ctc	ccg	gag	cct	gcc	acc	ctg	ggc	ttc	tcg	gca	557
Lys	Asp	Arg	Gln	Arg	Leu	Pro	Glu	Pro	Ala	Thr	Leu	Gly	Phe	Ser	Ala	
	95					100					105					
cgg	ggg	cag	ggg	ctg	gag	ctg	ggc	ctc	ccc	tcc	act	cca	gga	acc	ccc	605
Arg	Gly	Gln	Gly	Leu	Glu	Leu	Gly	Leu	Pro	Ser	Thr	Pro	Gly	Thr	Pro	
110					115					120				125		
acg	ccc	acg	ccc	cac	acc	tcc	ctg	ggc	tcc	cct	gtg	tca	tcc	gac	ccg	653
Thr	Pro	Thr	Pro	His	Thr	Ser	Leu	Gly	Ser	Pro	Val	Ser	Ser	Asp	Pro	
				130					135				140			
gtg	cac	atg	tcg	ccc	ctg	gag	ccc	cgg	gga	ggg	caa	ggc	gac	ggc	ctc	701
Val	His	Met	Ser	Pro	Leu	Glu	Pro	Arg	Gly	Gly	Gln	Gly	Asp	Gly	Leu	
			145					150				155				
gcc	ctt	gtg	ctg	atc	ctg	gcg	ttc	tgt	gtg	gcc	ggt	gca	gcc	gcc	ctc	749
Ala	Leu	Val	Leu	Ile	Leu	Ala	Phe	Cys	Val	Ala	Gly	Ala	Ala	Ala	Leu	
		160				165					170					
tcc	gta	gcc	tcc	ctc	tgc	tgg	tgc	agg	ctg	cag	cgt	gag	atc	cgc	ctg	797
Ser	Val	Ala	Ser	Leu	Cys	Trp	Cys	Arg	Leu	Gln	Arg	Glu	Ile	Arg	Leu	
		175				180					185					
act	cag	aag	gcc	gac	tac	gcc	act	gcg	aag	gcc	cct	ggc	tca	cct	gca	845
Thr	Gln	Lys	Ala	Asp	Tyr	Ala	Thr	Ala	Lys	Ala	Pro	Gly	Ser	Pro	Ala	
190					195					200				205		
gct	ccc	cgg	atc	tcg	cct	ggg	gac	cag	cgg	ctg	gca	cag	agc	gcg	gag	893

36

Ala Pro Arg Ile Ser Pro Gly Asp Gln Arg Leu Ala Gln Ser Ala Glu
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 atg tac cac tac cag cac caa cgg caa cag atg ctg tgc ctg gag cgg 941
 Met Tyr His Tyr Gln His Gln Arg Gln Gln Met Leu Cys Leu Glu Arg
 225 230 235
 cat aaa gag cca ccc aag gag ctg gac acg gcc tcc tgc gat gag gag 989
 His Lys Glu Pro Pro Lys Glu Leu Asp Thr Ala Ser Ser Asp Glu Glu
 240 245 250
 aat gag gac gga gac ttc acg gtg tac gag tgc ccg ggc ctg gcc ccg 1037
 Asn Glu Asp Gly Asp Phe Thr Val Tyr Glu Cys Pro Gly Leu Ala Pro
 255 260 265
 acc ggg gaa atg gag gtg cgc aac cct ctg ttc gac cac gcc gca ctg 1085
 Thr Gly Glu Met Glu Val Arg Asn Pro Leu Phe Asp His Ala Ala Leu
 270 275 280 285
 tcc ggc ccc ctg ccg gcc ccc agc tca ccg cct gca ctg cca 1127
 Ser Ala Pro Leu Pro Ala Pro Ser Ser Pro Pro Ala Leu Pro
 290 295
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 gggctccagg ccctgggacc ccttgccagg gagacccccg aacctttgtg ccaggacacc 1307
 tcttggtccc ctgcacctct cctgtttggt ttagaccccc aaactggagg gggcatggag 1367
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<211> 1556

<212> DNA

<213> Homo Sapiens

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<222> 261..1166

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<221> sig_peptide

<222> 261..314

<223> Von Heijne matrix

score 8.80

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<222> 1524..1556

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cgaaccccag cctgcacgcc cggtttagcat tcggccggga gatgcggcag tggaatctgg	120		
aagggcgggtg aaaaacctac gtcctgccct cggccggcct ctccattcgt ccccgggta	180		
gagaggtgcc cggtccccc cccctccag cccagccct ggagacagca gccctagac	240		
tactgaggga cagcgacagc atg aag gct ccg ggt cgg ctc gtg ctc atc atc	293		
Met Lys Ala Pro Gly Arg Leu Val Leu Ile Ile			
-15	-10		
ctg tgc tcc gtg gtc ttc tct gcc gtc tac atc ctc ctg tgc tgc tgg	341		
Leu Cys Ser Val Val Phe Ser Ala Val Tyr Ile Leu Leu Cys Cys Trp			
-5	1	5	
gcc ggc ctg ccc ctc tgc ctg gcc acc tgc ctg gac cac cac ttc ccc	389		
Ala Gly Leu Pro Leu Cys Leu Ala Thr Cys Leu Asp His His Phe Pro			
10	15	20	25
aca ggc tcc agg ccc act gtg ccg gga ccc ctg cac ttc agt gga tat	437		
Thr Gly Ser Arg Pro Thr Val Pro Gly Pro Leu His Phe Ser Gly Tyr			
30	35	40	
agc agt gtg cca gat ggg aag ccg ctg gtc cgc gag ccc tgc cgc agc	485		
Ser Ser Val Pro Asp Gly Lys Pro Leu Val Arg Glu Pro Cys Arg Ser			
45	50	55	
tgt gcc gtg gtg tcc agc tcc ggc caa atg ctg ggc tca ggc ctg ggt	533		
Cys Ala Val Val Ser Ser Ser Gly Gln Met Leu Gly Ser Gly Leu Gly			
60	65	70	
gct gag atc gac agt gcc gag tgc gtg ttc cgc atg aac cag gcg ccc	581		
Ala Glu Ile Asp Ser Ala Glu Cys Val Phe Arg Met Asn Gln Ala Pro			
75	80	85	
acc gtg ggc ttt gag gcg gat gtg ggc cag cgc agc acc ctg cgt gtc	629		
Thr Val Gly Phe Glu Ala Asp Val Gly Gln Arg Ser Thr Leu Arg Val			
90	95	100	105
gtc tca cac aca agc gtg ccg ctg ctg ctg cgc aac tat tca cac tac	677		
Val Ser His Thr Ser Val Pro Leu Leu Leu Arg Asn Tyr Ser His Tyr			
110	115	120	
ttc cag aag gcc cga gac acg ctc tac atg gtg tgg ggc cag ggc agg	725		
Phe Gln Lys Ala Arg Asp Thr Leu Tyr Met Val Trp Gly Gln Gly Arg			
125	130	135	
cac atg gac cgg gtg ctc ggc ggc cgc acc tac cgc acg ctg ctg cag	773		
His Met Asp Arg Val Leu Gly Gly Arg Thr Tyr Arg Thr Leu Leu Gln			
140	145	150	
ctc acc agg atg tac ccc ggc ctg cag gtg tac acc ttc acg gag cgc	821		
Leu Thr Arg Met Tyr Pro Gly Leu Gln Val Tyr Thr Phe Thr Glu Arg			


```
155          160          165
atg atg gcc tac tgc gac cag atc ttc cag gac gag acg ggc aag aac      869
Met Met Ala Tyr Cys Asp Gln Ile Phe Gln Asp Glu Thr Gly Lys Asn
170          175          180          185
cgg agg cag tcg ggc tcc ttc ctc agc acc ggc tgg ttc acc atg atc      917
Arg Arg Gln Ser Gly Ser Phe Leu Ser Thr Gly Trp Phe Thr Met Ile
190          195          200
ctc gcg ctg gag ctg tgt gag gag atc gtg gtc tat ggg atg gtc agc      965
Leu Ala Leu Glu Leu Cys Glu Glu Ile Val Val Tyr Gly Met Val Ser
205          210          215
gac agc tac tgc agg gag aag agc cac ccc tca gtg cct tac cac tac      1013
Asp Ser Tyr Cys Arg Glu Lys Ser His Pro Ser Val Pro Tyr His Tyr
220          225          230
ttt gag aag ggc cgg cta gat gag tgt cag atg tac ctg gca cac gag      1061
Phe Glu Lys Gly Arg Leu Asp Glu Cys Gln Met Tyr Leu Ala His Glu
235          240          245
cag gcg ccc cga agc gcc cac cgc ttc atc act gag aag gcg gtc ttc      1109
Gln Ala Pro Arg Ser Ala His Arg Phe Ile Thr Glu Lys Ala Val Phe
250          255          260          265
tcc cgc tgg gcc aag aag agg ccc atc gtg ttc gcc cat ccg tcc tgg      1157
Ser Arg Trp Ala Lys Lys Arg Pro Ile Val Phe Ala His Pro Ser Trp
270          275          280
agg act gag tagcttccgt cgtcctgcc a gccgccatgc cgttgcgagg      1206
Arg Thr Glu
cctccgggat gtcccatccc aagccatcac actccactcc ctgagtaatt catggcattt      1266
ggggggctcac cacctccagg tctgtcaagt ggcctttgtc cctggggctg atggcccca      1326
actcaccagc atcatgacct tgtgccagtc ctggtcctcc ctccccagcc gccctacca      1386
ccttttggtg ccacacttct caggctggcc gccctgggtg gggcagccga gagcctgggg      1446
ttcattggtg aaggggcctt ggagttgtga ctgccggggc cgtatcagga acgtacgggt      1506
aaacgtgtgt tttctggaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa      1556
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<210> 26
<211> 1058
<212> DNA
<213> Homo Sapiens

<220>
<221> CDS
<222> 67..813

<220>
<221> sig_peptide

<222> 67..111

<223> Von Heijne matrix

score 5.20

seq QLWKLVLCCGVLT/GT

<220>

<221> polyA_signal

<222> 1023..1028

<220>

<221> polyA_site

<222> 1042..1058

<400> 26

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agcagactgt gcagtggggc aaggatttca tgagcatcct cctctaaacg cgtgacaaga      60
caaaag atg ctt cag ctt tgg aaa ctt gtt ctc ctg tgc ggc gtg ctc      108
      Met Leu Gln Leu Trp Lys Leu Val Leu Leu Cys Gly Val Leu
      -15          -10          -5
act ggg acc tca gag tct ctt ctt gac aat ctt ggc aat gac cta agc      156
Thr Gly Thr Ser Glu Ser Leu Leu Asp Asn Leu Gly Asn Asp Leu Ser
      1          5          10          15
aat gtc gtg gat aag ctg gaa cct gtt ctt cac gag gga ctt gag aca      204
Asn Val Val Asp Lys Leu Glu Pro Val Leu His Glu Gly Leu Glu Thr
      20          25          30
gtt gac aat act ctt aaa ggc atc ctt gag aaa ctg aag gtc gac cta      252
Val Asp Asn Thr Leu Lys Gly Ile Leu Glu Lys Leu Lys Val Asp Leu
      35          40          45
gga gtg ctt cag aaa tcc agt gct tgg caa ctg gcc aag cag aag gcc      300
Gly Val Leu Gln Lys Ser Ser Ala Trp Gln Leu Ala Lys Gln Lys Ala
      50          55          60
cag gaa gct gag aaa ttg ctg aac aat gtc att tct aag ctg ctt cca      348
Gln Glu Ala Glu Lys Leu Leu Asn Asn Val Ile Ser Lys Leu Leu Pro
      65          70          75
act aac acg gac att ttt ggg ttg aaa atc agc aac tcc ctc atc ctg      396
Thr Asn Thr Asp Ile Phe Gly Leu Lys Ile Ser Asn Ser Leu Ile Leu
      80          85          90          95
gat gtc aaa gct gaa ccg atc gat gat ggc aaa ggc ctt aac ctg agc      444
Asp Val Lys Ala Glu Pro Ile Asp Asp Gly Lys Gly Leu Asn Leu Ser
      100          105          110
ttc cct gtc acc gcg aat gtc act gtg gcc ggg ccc atc att ggc cag      492
Phe Pro Val Thr Ala Asn Val Thr Val Ala Gly Pro Ile Ile Gly Gln
      115          120          125

```

att atc aac ctg aaa gcc tcc ttg gac ctc ctg acc gca gtc aca att 540
Ile Ile Asn Leu Lys Ala Ser Leu Asp Leu Leu Thr Ala Val Thr Ile
130 135 140
gaa act gat ccc cag aca cac cag cct gtt gcc gtc ctg gga gaa tgc 588
Glu Thr Asp Pro Gln Thr His Gln Pro Val Ala Val Leu Gly Glu Cys
145 150 155
gcc agt gac cca acc agc atc tca ctt tcc ttg ctg gac aaa cac agc 636
Ala Ser Asp Pro Thr Ser Ile Ser Leu Ser Leu Leu Asp Lys His Ser
160 165 170 175
caa atc atc aac aag ttc gtg aat agc gtg atc aac acg ctg aaa agc 684
Gln Ile Ile Asn Lys Phe Val Asn Ser Val Ile Asn Thr Leu Lys Ser
180 185 190
act gta tcc tcc ctg ctg cag aag gag ata tgt cca ctg atc cgc atc 732
Thr Val Ser Ser Leu Leu Gln Lys Glu Ile Cys Pro Leu Ile Arg Ile
195 200 205
ttc atc cac tcc ctg gat gtg aat gtc att cag cag gtc gtc gat aat 780
Phe Ile His Ser Leu Asp Val Asn Val Ile Gln Gln Val Val Asp Asn
210 215 220
cct cag cac aaa acc cag ctg caa acc ctc atc tgaagaggac gaatgaggag 833
Pro Gln His Lys Thr Gln Leu Gln Thr Leu Ile
225 230
gaccactgtg gtgcatgctg attggttccc agtggcttgc cccaccccct tatagcatct 893
ccctccagga agctgctgcc accacctaac cagcgtgaaa gcctgagtc caccagaagg 953
accttcccag ataccccttc tctcacagt cagaacagca gcctctacac atgttgtcct 1013
gccccctggca ataaaggccc atttctgcaa aaaaaaaaaa aaaaa 1058

<210> 27

<211> 648

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 187..438

<220>

<221> polyA_signal

<222> 612..617

<220>

<221> polyA_site

<222> 632..648

<400> 27

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agtgcgcact ggcgtgcgag actcggcggg cgctgttgag ggagtcgggc cgcgactgtg      60
gtcgttttta taccttcccg cgcggacgcc ggcgctgcca acggaagggc ggagacggag      120
tttcgtcatg ttggccaggc ccatttgaga tctttgaaga taccctcaac gtgaggctct      180
gctgcc atg aag gtg aag att aag tgc tgg aac ggc gtg gcc act tgg      228
      Met Lys Val Lys Ile Lys Cys Trp Asn Gly Val Ala Thr Trp
          1             5             10
ctc tgg gtg gcc aac gat gag aac tgt ggc atc tgc agg atg gca ttt      276
Leu Trp Val Ala Asn Asp Glu Asn Cys Gly Ile Cys Arg Met Ala Phe
15             20             25             30
aac gga tgc tgc cct gac tgc aag gtg ccc ggc gac gac tgc ccg ctg      324
Asn Gly Cys Cys Pro Asp Cys Lys Val Pro Gly Asp Asp Cys Pro Leu
          35             40             45
gtg tgg ggc cag tgc tcc cac tgc ttc cac atg cat tgc atc ctc aag      372
Val Trp Gly Gln Cys Ser His Cys Phe His Met His Cys Ile Leu Lys
          50             55             60
tgg ctg cac gca cag cag gtg cag cag cac tgc ccc atg tgc cgc cag      420
Trp Leu His Ala Gln Gln Val Gln Gln His Cys Pro Met Cys Arg Gln
          65             70             75
gaa tgg aag ttc aag gag tgaggcccca cctggctctc gctggagggg      468
Glu Trp Lys Phe Lys Glu
          80
catcctgaga ctccctcctc atgctggcgc cgatggctgc tggggacagc gcccctgagc      528
tgcaacaagg tggaaacaag ggctggagct gcgtttgttt tgccatcact atgttgacac      588
ttttatccaa taagtgaata ctcattaaac tactcaaata tcgaaaaaaaa aaaaaaaaaa      648

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<210> 28

<211> 2104

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 92..1753

<220>

<221> sig_peptide

<222> 92..130

<223> Von Heijne matrix

score 3.90

seq MLYLQGWSMPAVA/EV

<220>

<221> polyA_signal

<222> 2070..2075

<220>

<221> polyA_site

<222> 2090..2104

<220>

<221> misc_feature

<222> 905

<223> n=a, g, c or t

<220>

<221> unsure

<222> 259

<223> Xaa = Asp,His,Asn,Tyr

<400> 28

atagacttta tcatacttcg tagcatcag tatgtttct ttgctaagat tattgatttt 60
gtattgaagg gtcccatgtc catcgttttc a atg ctt tat ctc cag ggt tgg 112
Met Leu Tyr Leu Gln Gly Trp

-10

agc atg cct gct gtg gca gag gta aaa ctt cga gat gat caa tat aca 160
Ser Met Pro Ala Val Ala Glu Val Lys Leu Arg Asp Asp Gln Tyr Thr

-5 1 5 10
ctg gaa cac atg cat gct ttt gga atg tat aat tac ctg cac tgt gat 208
Leu Glu His Met His Ala Phe Gly Met Tyr Asn Tyr Leu His Cys Asp

15 20 25
tca tgg tat caa gac agt gtc tac tat att gat acc ctt gga aga att 256
Ser Trp Tyr Gln Asp Ser Val Tyr Tyr Ile Asp Thr Leu Gly Arg Ile

30 35 40
atg aat tta aca gta atg ctg gac act gcc tta gga aaa cca cga gag 304
Met Asn Leu Thr Val Met Leu Asp Thr Ala Leu Gly Lys Pro Arg Glu

45 50 55
gtg ttt cga ctt cct aca gat ttg aca gca tgt gac aac cgt ctt tgt 352
Val Phe Arg Leu Pro Thr Asp Leu Thr Ala Cys Asp Asn Arg Leu Cys

60 65 70
gca tct atc cat ttc tca tct tct acc tgg gtt acc ttg tca gat gga 400
Ala Ser Ile His Phe Ser Ser Ser Thr Trp Val Thr Leu Ser Asp Gly
75 80 85 90

act gga aga ttg tat gtc att gga aca ggt gaa cgt gga aat agc gct	448
Thr Gly Arg Leu Tyr Val Ile Gly Thr Gly Glu Arg Gly Asn Ser Ala	
95 100 105	
tct gaa aaa tgg gag att atg ttt aat gaa gaa ctt ggg gat cct ttt	496
Ser Glu Lys Trp Glu Ile Met Phe Asn Glu Glu Leu Gly Asp Pro Phe	
110 115 120	
att ata att cac agt atc tca ctg cta aat gct gaa gaa cat tct ata	544
Ile Ile Ile His Ser Ile Ser Leu Leu Asn Ala Glu Glu His Ser Ile	
125 130 135	
gct acc cta ctt ctt cga ata gag aaa gag gaa ttg gat atg aaa gga	592
Ala Thr Leu Leu Leu Arg Ile Glu Lys Glu Glu Leu Asp Met Lys Gly	
140 145 150	
agt ggt ttc tat gtt tct ctg gag tgg gtc act atc agt aag aaa aat	640
Ser Gly Phe Tyr Val Ser Leu Glu Trp Val Thr Ile Ser Lys Lys Asn	
155 160 165 170	
caa gat aat aaa aaa tat gaa att att aag cgt gat att ctc cgt gga	688
Gln Asp Asn Lys Lys Tyr Glu Ile Ile Lys Arg Asp Ile Leu Arg Gly	
175 180 185	
aag tca gtg cca cat tat gct gct att aag cct gat gga aat ggt cta	736
Lys Ser Val Pro His Tyr Ala Ala Ile Lys Pro Asp Gly Asn Gly Leu	
190 195 200	
atg att gta tcc tac aag tct tta aca ttt gtt cag gct ggt caa gat	784
Met Ile Val Ser Tyr Lys Ser Leu Thr Phe Val Gln Ala Gly Gln Asp	
205 210 215	
ctt gaa gaa aat atg gat gaa gac ata tca gag aaa atc aaa gaa cct	832
Leu Glu Glu Asn Met Asp Glu Asp Ile Ser Glu Lys Ile Lys Glu Pro	
220 225 230	
ctg tat tac tgg caa cag act gaa gat gat ttg aca gta acc ata cgg	880
Leu Tyr Tyr Trp Gln Gln Thr Glu Asp Asp Leu Thr Val Thr Ile Arg	
235 240 245 250	
ctt cca gaa gac agt act aag gag nac att caa ata cag ttt ttg cct	928
Leu Pro Glu Asp Ser Thr Lys Glu Xaa Ile Gln Ile Gln Phe Leu Pro	
255 260 265	
gat cac atc aac att gta ctg aag gat cac cag ttt tta gaa gga aaa	976
Asp His Ile Asn Ile Val Leu Lys Asp His Gln Phe Leu Glu Gly Lys	
270 275 280	
ctc tat tca tct att gat cat gaa agc agt aca tgg ata att aaa gag	1024
Leu Tyr Ser Ser Ile Asp His Glu Ser Ser Thr Trp Ile Ile Lys Glu	
285 290 295	
agt aat agc ttg gag att tcc ttg att aag aag aat gaa gga ctg acc	1072
Ser Asn Ser Leu Glu Ile Ser Leu Ile Lys Lys Asn Glu Gly Leu Thr	
300 305 310	

aca gag aat taattattct aacatattgg cctcttttga ctggaaaagt 1793
Thr Glu Asn

540

attcagtggt acctggaggt ctggacagtt atactgtaac ctcttaagtt ttaatgtgct 1853
aaatatatct tgtatgattt tttatttttt aataacattg gaaatatatt caagagatta 1913
tgattctgta aagctgtgga atgaagctgc agatttagag aacattggct tctgaaaaaa 1973
aaaaagagtg aagatagtag tagcaagtat acttattttt taaaacaggc tagaatctca 2033
tgtttttatat gaaagatgta caattcagtg tttaaaaata aaaatattta ttgtgtaaaa 2093
aaaaaaaaaa a 2104

<210> 29

<211> 515

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 144..440

<220>

<221> sig_peptide

<222> 144..287

<223> Von Heijne matrix

score 4.10

seq VFMLIVSVLALIP/ET

<220>

<221> polyA_signal

<222> 457..462

<220>

<221> polyA_site

<222> 500..515

<220>

<221> misc_feature

<222> 60

<223> n=a, g, c or t

<400> 29

agagagcggg aagccgagct gggcgagaag taggggaggg cggtgctccg cgcggtggcn 60
gttgctatcg ctctgcagaa cctactcagg cagccagctg agaagagttg agggaaagtg 120


```

ctgctgctgg gtctgcagac gcg atg gat aac gtg cag ccg aaa ata aaa cat    173
                               Met Asp Asn Val Gln Pro Lys Ile Lys His
                               -45                               -40

cgc ccc ttc tgc ttc agt gtg aaa ggc cac gtg aag atg ctg cgg ctg    221
Arg Pro Phe Cys Phe Ser Val Lys Gly His Val Lys Met Leu Arg Leu
                               -35                               -30                               -25

gat att atc aac tca ctg gta aca aca gta ttc atg ctc atc gta tct    269
Asp Ile Ile Asn Ser Leu Val Thr Thr Val Phe Met Leu Ile Val Ser
                               -20                               -15                               -10

gtg ttg gca ctg ata cca gaa acc aca aca ttg aca gtt ggt gga ggg    317
Val Leu Ala Leu Ile Pro Glu Thr Thr Thr Leu Thr Val Gly Gly Gly
                               -5                               1                               5                               10

gtg ttt gca ctt gtg aca gca gta tgc tgt ctt gcc gac ggg gcc ctt    365
Val Phe Ala Leu Val Thr Ala Val Cys Cys Leu Ala Asp Gly Ala Leu
                               15                               20                               25

att tac cgg aag ctt ctg ttc aat ccc agc ggt cct tac cag aaa aag    413
Ile Tyr Arg Lys Leu Leu Phe Asn Pro Ser Gly Pro Tyr Gln Lys Lys
                               30                               35                               40

cct gtg cat gaa aaa aaa gaa gtt ttg taattttata ttacttttta    460
Pro Val His Glu Lys Lys Glu Val Leu
                               45                               50

gtttgatact aagtattaaa catatttctg tattcttcca aaaaaaaaaa aaaat    515

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<210> 30

<211> 661

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 174..443

<220>

<221> sig_peptide

<222> 174..269

<223> Von Heijne matrix

score 4.10

seq SSLAFCQVGFLTA/QP

<220>

<221> polyA_signal

<222> 623..628

<220>

<221> polyA_site

<222> 647..661

<400> 30

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aaaaaggaac tttcagtgat aatgaacaaa actcaggagc tatgtggatg acaggagcac      60
ctagatgacc gactttaccc acttcaaatg ctaccttgac cctagcactc tctccaccct      120
gcacctcac ctcagaccat cagttggta ggccaacagc tcaccatcaa ttc atg      176
                                     Met
ccc tgc cta gac caa cag etc act gtt cat gcc cta ccc tgc cct gcc      224
Pro Cys Leu Asp Gln Gln Leu Thr Val His Ala Leu Pro Cys Pro Ala
      -30                -25                -20
cag ccc tcc tct ctg gcc ttc tgc caa gtg ggg ttc tta aca gca cag      272
Gln Pro Ser Ser Leu Ala Phe Cys Gln Val Gly Phe Leu Thr Ala Gln
      -15                -10                -5                1
cct tca cct ccg aga agg cgc aat ggg aaa gac aga tac acg ttg gtt      320
Pro Ser Pro Pro Arg Arg Arg Asn Gly Lys Asp Arg Tyr Thr Leu Val
              5                10                15
ctg caa cac cag gaa tgc cag gat gat tta gcc acc tcc tca ctt gtc      368
Leu Gln His Gln Glu Cys Gln Asp Asp Leu Ala Thr Ser Ser Leu Val
              20                25                30
tac ctt tcc etc ccc tgc ttc aaa gac ttg ggt cga tgc aag cac caa      416
Tyr Leu Ser Leu Pro Cys Phe Lys Asp Leu Gly Arg Ser Lys His Gln
              35                40                45
agc atc act gtt gct gac act aac aag tagtgccaag ggattgcctt      463
Ser Ile Thr Val Ala Asp Thr Asn Lys
50                55
taaggaagat caggagcgga acatctggtg gcaaagaaaa tctttctaata agcccatc      523
tagtgaccac cttcaacctc ctcatagcag gagagtttgg gagtagggga cttaggatgt      583
tttgttcttt taatcaattc agaaaatatg tatgtttgaa ataaaaataa aaatacttga      643
gccaaaaaaa aaaaaaaaaa      661

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<210> 31

<211> 694

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 55..399

<220>

<221> sig_peptide

<222> 55..192

<223> Von Heijne matrix

score 4.70

seq ILTGLTVGSAADA/GE

<220>

<221> polyA_signal

<222> 654..659

<220>

<221> polyA_site

<222> 680..694

<400> 31

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aatgcttgag gaaaactggg aacagtatat tgttctgaaa acctaaaaag ttta atg      57
                                                    Met
aaa acc ttg ttc aat cca gcc cct gcc att gct gac ctg gat ccc cag      105
Lys Thr Leu Phe Asn Pro Ala Pro Ala Ile Ala Asp Leu Asp Pro Gln
-45              -40              -35              -30
ttc tac acc ctc tca gat gtg ttc tgc tgc aat gaa agt gag gct gag      153
Phe Tyr Thr Leu Ser Asp Val Phe Cys Cys Asn Glu Ser Glu Ala Glu
              -25              -20              -15
att tta act ggc ctc acg gtg ggc agc gct gca gat gct ggg gag gct      201
Ile Leu Thr Gly Leu Thr Val Gly Ser Ala Ala Asp Ala Gly Glu Ala
              -10              -5              1
gca tta gtg ctc ttg aaa agg ggc tgc cag gtg gta atc att acc tta      249
Ala Leu Val Leu Leu Lys Arg Gly Cys Gln Val Val Ile Ile Thr Leu
              5              10              15
ggg gct gaa gga tgt gtg gtg ctg tca cag aca gaa cct gag cca aag      297
Gly Ala Glu Gly Cys Val Val Leu Ser Gln Thr Glu Pro Glu Pro Lys
20              25              30              35
cac att ccc aca gag aaa gtc aag gct gtg gat acc acg tgt aga cct      345
His Ile Pro Thr Glu Lys Val Lys Ala Val Asp Thr Thr Cys Arg Pro
              40              45              50
ggc tca aga ccc aag agt gaa gca gca agt gtg aag aag cag aaa cat      393
Gly Ser Arg Pro Lys Ser Glu Ala Ala Ser Val Lys Lys Gln Lys His
              55              60              65
tat aaa taaccagag aatcctttta taacagcaac tgccactga tttgtggcc      449
Tyr Lys
taacagctcg agcaaaaatg aatataaata caacattgtg caatgactaa ttactcaaaa      509

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ttttgtgcat cagcagaagt ggaacctgtg gttggtgcta atattatgaa atgcctttgc 569
tgtttaataa tctggtagct ctgtattatt tagcatgcat ttttcttgga gaacaatgat 629
tttatttcaa gtacctctca ctgaaataaa aaagcagctg ttagaagacg aaaaaaaaaa 689
aaaaa 694
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<210> 32

<211> 1110

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 90..287

<220>

<221> sig_peptide

<222> 90..146

<223> Von Heijne matrix

score 9.30

seq VFVFLFLWDPVLA/GI

<220>

<221> polyA_signal

<222> 1078..1083

<220>

<221> polyA_site

<222> 1096..1110

<400> 32

atcatcttac atcagcacia gaagaagagt gagcatagca caccgatgtc agaccctgcc 60

actagcctcc ttaacagaag ttcccagcc atg aag cct ctc ctt gtt gtg ttt 113

Met Lys Pro Leu Leu Val Val Phe

-15

gtc ttt ctt ttc ctt tgg gat cca gtg ctg gca ggt ata aat tca tta 161

Val Phe Leu Phe Leu Trp Asp Pro Val Leu Ala Gly Ile Asn Ser Leu

-10

-5

1

5

tca tca gaa atg cac aag aaa tgc tat aaa aat ggc atc tgc aga ctt 209

Ser Ser Glu Met His Lys Lys Cys Tyr Lys Asn Gly Ile Cys Arg Leu

10

15

20

gaa tgc tat gag agt gaa atg tta gtt gcc tac tgt atg ttt cag ctg 257

Glu Cys Tyr Glu Ser Glu Met Leu Val Ala Tyr Cys Met Phe Gln Leu

```

                25                30                35
gag tgc tgt gtc aaa gga aat cct gca ccc tgacataaga aaccaatgaa 307
Glu Cys Cys Val Lys Gly Asn Pro Ala Pro

                40                45
tggccactat cctgtaggcc cttgattctg ccatctttca caaaaccagg gaatttagat 367
caaactgtga caccatgatg tgtccatgac tactggtttt tagcattttt ataggccagc 427
agactcttgt ggtcttaaat ttaaagagct gagctgtagc cttctttaaa agagctcggt 487
ttttcacaaa aacaatgtag aagatatttt ctcacctcaa cgtgatgtcc agtgtgtcca 547
tcagcacctg tttctccctc taatcataga ggatattctt attatttaga aaggcttcaa 607
gggaacaac ttttggcacc taagtcgtgt cctaccttcg cttcagcttc gcatttccca 667
tttctgtgaa attcccaact ttagagaagc agatttgcca tggccttctg acaaccttgt 727
acatctctca cataaacgcg ataggcaggg cttactaca ggctggcccg agtctggact 787
gagctcgacc ctgaagtcc tttggaacag gagaggccat cttgtgatgg gctggaacaa 847
ggtaatttct catccacctc cctagtttca gttgagcaat ggaacttccc acctgagccc 907
ctagggttca gctacaggct ataagactgc cgtcctgtgg tttagtgttg gttccttagc 967
agcagagtga tgcacctctc gctgcccgtc atctgactcc tctggatggg tgttatcctg 1027
tggcttaaga gctaacacca tgctgatctt gctttgctat atgtgtaact aataaactgc 1087
ctaaatgcaa aaaaaaaaaa aaa 1110
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<210> 33

<211> 623

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 49..447

<220>

<221> sig_peptide

<222> 49..111

<223> Von Heijne matrix

score 5.00

seq LIVIFFYCWLSSS/HE

<220>

<221> polyA_signal

<222> 579..584

<220>

<221> polyA_site

<222> 602..623

<400> 33

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attagaattt tctttctcaa attaaagggt tgagaaattc gtgatgag atg tcc tgt      57
                                     Met Ser Cys
                                     -20
tcc cta aag ttt act ttg att gta att ttt ttt tac tgt tgg ctt tca      105
Ser Leu Lys Phe Thr Leu Ile Val Ile Phe Phe Tyr Cys Trp Leu Ser
      -15                      -10                      -5
tcc agc cat gag gag tta gaa ggt ggt aca tgc aag tct ttt gac ctc      153
Ser Ser His Glu Glu Leu Glu Gly Gly Thr Ser Lys Ser Phe Asp Leu
      1                      5                      10
cat aca gtg att atg ctt gtc atc gct ggt ggt atc ctg gcg gcc ttg      201
His Thr Val Ile Met Leu Val Ile Ala Gly Gly Ile Leu Ala Ala Leu
      15                      20                      25                      30
ctc ctg ctg ata gtt gtc gtg ctc tgt ctt tac ttc aaa ata cac aac      249
Leu Leu Leu Ile Val Val Val Leu Cys Leu Tyr Phe Lys Ile His Asn
      35                      40                      45
gcg cta aaa gct gca aag gaa cct gaa gct gtg gct gta aaa aat cac      297
Ala Leu Lys Ala Ala Lys Glu Pro Glu Ala Val Ala Val Lys Asn His
      50                      55                      60
aac cca gac aag gtg tgg tgg gcc aag aac agc cag gcc aaa acc att      345
Asn Pro Asp Lys Val Trp Trp Ala Lys Asn Ser Gln Ala Lys Thr Ile
      65                      70                      75
gcc acg gag tct tgt cct gcc ctg cag tgc tgt gaa gga tat aga atg      393
Ala Thr Glu Ser Cys Pro Ala Leu Gln Cys Cys Glu Gly Tyr Arg Met
      80                      85                      90
tgt gcc agt ttt gat tcc ctg cca cct tgc tgt tgc gac ata aat gag      441
Cys Ala Ser Phe Asp Ser Leu Pro Pro Cys Cys Cys Asp Ile Asn Glu
      95                      100                      105                      110
ggc ctc tgagtttaga aaggtgggca caaaaatctt catgagcaat acttcttagt      497
Gly Leu
agattgtttt gttattcaaa tcaagttcta gtgtttttat gtgagattat ataatttaca      557
gtgtgttttt atatactttt gaataaatgt acactattaa aaataaaaaa aaaaaaaaat      617
gccaaa                                           623

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<210> 34

<211> 657

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 199..618

<220>

<221> sig_peptide

<222> 199..408

<223> Von Heijne matrix

score 3.90

seq FKVLTQPLSLLWG/CD

<220>

<221> polyA_signal

<222> 626..631

<220>

<221> polyA_site

<222> 643..657

<400> 34

aactggatag agtactgcc ccttcagccc atggagaaa gcaaatgcct ccttcagagt	60
ctacctaatg ctttctcaga taaataagca tgaagaaaag tcaaagtcca ttctagctct	120
aaaataagga atgaaatgtt ttctgatata gattttttgt tttcatctga taataatatt	180
atatatcaca gaaacagc atg gtt ctt act aaa cct ctt caa aga aat ggc	231
Met Val Leu Thr Lys Pro Leu Gln Arg Asn Gly	
-70 -65 -60	
agc atg atg agc ttt gaa aat gtg aaa gaa aag agc aga gaa gga ggg	279
Ser Met Met Ser Phe Glu Asn Val Lys Glu Lys Ser Arg Glu Gly Gly	
-55 -50 -45	
ccc cat gca cac aca ccc gaa gaa gaa ttg tgt ttc gtg gta aca cac	327
Pro His Ala His Thr Pro Glu Glu Glu Leu Cys Phe Val Val Thr His	
-40 -35 -30	
tac cct cag gtt cag acc aca ctc aac ctg ttt ttc cat ata ttc aag	375
Tyr Pro Gln Val Gln Thr Thr Leu Asn Leu Phe Phe His Ile Phe Lys	
-25 -20 -15	
gtt ctt act caa cca ctt tcc ctt ctg tgg ggt tgt gat cag aag cct	423
Val Leu Thr Gln Pro Leu Ser Leu Leu Trp Gly Cys Asp Gln Lys Pro	
-10 -5 1 5	
cgt act gtt cct acc ctt gga aac ggc gca tgg gat acc tgc caa caa	471
Arg Thr Val Pro Thr Leu Gly Asn Gly Ala Trp Asp Thr Cys Gln Gln	
10 15 20	
cac ata cgc act tca tca tgg aca gca aac aca ctc gtc att caa aac	519
His Ile Arg Thr Ser Ser Trp Thr Ala Asn Thr Leu Val Ile Gln Asn	
25 30 35	

53

```

cag cat tca cgg gaa agc act gtt tct gtt tgc ctt ttt atg tta atc      567
Gln His Ser Arg Glu Ser Thr Val Ser Val Cys Leu Phe Met Leu Ile
      40              45              50
cgc atg caa cat att ttg aaa aca gat aca ctt caa cag ttc aga ata      615
Arg Met Gln His Ile Leu Lys Thr Asp Thr Leu Gln Gln Phe Arg Ile
      55              60              65
tgc tagtactaat aaaaccaaca tgtaaaaaaa aaaaaaaaaa      657
Cys
70

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<210> 35

<211> 1137

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 271..969

<220>

<221> sig_peptide

<222> 271..366

<223> Von Heijne matrix

score 5.60

seq WMGLACFRSLAAS/SP

<220>

<221> polyA_signal

<222> 1092..1097

<220>

<221> polyA_site

<222> 1123..1137

<400> 35

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aaaaaccttt caagtgtccc ctccttttct taaagtcttt tataggggtc cccttcttgg      60
ccatctccat cctgtgagtc aggactgaaa gggcacagac aggtcactgc cagcattgtt      120
ggggcaagcc tgcaagcacg catcactggg gatctgacat gacaatggcc gcctgtcccc      180
tctgagggct acaggactta cccagtgagg aagcagctaa gcaggtctga ccagccgacc      240
tggacctggc caagggctct gtcacccctc atg gcc acc ccg cca ttc cgg ctg      294
Met Ala Thr Pro Pro Phe Arg Leu

```


ata agg aag atg ttt tcc ttc aag gtg agc aga tgg atg ggg ctt gcc	342
Ile Arg Lys Met Phe Ser Phe Lys Val Ser Arg Trp Met Gly Leu Ala	
-20 -15 -10	
tgc ttc cgg tcc ctg gcg gca tcc tct ccc agt att cgc cag aag aaa	390
Cys Phe Arg Ser Leu Ala Ala Ser Ser Pro Ser Ile Arg Gln Lys Lys	
-5 1 5	
cta atg cac aag ctg cag gag gaa aag gct ttt cgc gaa gag atg aaa	438
Leu Met His Lys Leu Gln Glu Lys Ala Phe Arg Glu Glu Met Lys	
10 15 20	
att ttt cgt gaa aaa ata gag gac ttc agg gaa gag atg tgg act ttc	486
Ile Phe Arg Glu Lys Ile Glu Asp Phe Arg Glu Glu Met Trp Thr Phe	
25 30 35 40	
cga ggc aag atc cat gct ttc cgg ggc cag atc ctg ggt ttt tgg gaa	534
Arg Gly Lys Ile His Ala Phe Arg Gly Gln Ile Leu Gly Phe Trp Glu	
45 50 55	
gag gag aga cct ttc tgg gaa gag gag aaa acc ttc tgg aaa gag gaa	582
Glu Glu Arg Pro Phe Trp Glu Glu Glu Lys Thr Phe Trp Lys Glu Glu	
60 65 70	
aaa tcc ttc tgg gaa atg gaa aag tct ttc agg gag gaa gag aaa act	630
Lys Ser Phe Trp Glu Met Glu Lys Ser Phe Arg Glu Glu Lys Thr	
75 80 85	
ttc tgg aaa aag tac cgc act ttc tgg aag gag gat aag gcc ttc tgg	678
Phe Trp Lys Lys Tyr Arg Thr Phe Trp Lys Glu Asp Lys Ala Phe Trp	
90 95 100	
aaa gag gac aat gcc tta tgg gaa aga gac cgg aac ctt ctt cag gag	726
Lys Glu Asp Asn Ala Leu Trp Glu Arg Asp Arg Asn Leu Leu Gln Glu	
105 110 115 120	
gac aag gcc ctg tgg gag gaa gaa aag gcc ctg tgg gta gag gaa aga	774
Asp Lys Ala Leu Trp Glu Glu Glu Lys Ala Leu Trp Val Glu Glu Arg	
125 130 135	
gcc ctc ctt gag ggg gag aaa gcc ctg tgg gaa gat aaa acg tcc ctc	822
Ala Leu Leu Glu Gly Glu Lys Ala Leu Trp Glu Asp Lys Thr Ser Leu	
140 145 150	
tgg gag gaa gag aat gcc ctc tgg gag gaa gag agg gcc ttc tgg atg	870
Trp Glu Glu Glu Asn Ala Leu Trp Glu Glu Glu Arg Ala Phe Trp Met	
155 160 165	
gag aac aat ggc cac att gcc gga gag cag atg ctc gaa gat ggg ccc	918
Glu Asn Asn Gly His Ile Ala Gly Glu Gln Met Leu Glu Asp Gly Pro	
170 175 180	
cac aac gcc aac aga ggg cag cgc ttg ctg gcc ttc tcc cga ggc agg	966
His Asn Ala Asn Arg Gly Gln Arg Leu Leu Ala Phe Ser Arg Gly Arg	
185 190 195 200	

gcg tagccagcat gcaggtgcag ggccctgtgg tccagaactcc cctgggttgg 1019
 Ala
 gattcaagtc caggggtgagc ccatgtgctg gagaaaatac acactcattg gtctccttgc 1079
 ttgtaaagat ccaataaagt cctgaggcaa ggtttggaac accaaaaaaa aaaaaaaa 1137

<210> 36

<211> 636

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 192..440

<220>

<221> sig_peptide

<222> 192..278

<223> Von Heijne matrix

score 5.20

seq VVFMTVAAGGASS/FA

<220>

<221> polyA_signal

<222> 590..595

<220>

<221> polyA_site

<222> 622..636

<400> 36

aaaagcgagt caggtccctc gcgctccgc cccacgcgcg tgaccagagc gcgctggccc 60

ggcccaccgc gggcggttgt ggtcgctata tataaggtgg ggaggccgcc ggcccgttcg 120

gttcggggcg ttaccatcgt ccgtgcgcac cgcggggcgt ccagatttgg caattcttcg 180

ctgaagtcac c atg agc ttt ttc caa ctg atg aaa agg aag gaa ctg 230

Met Ser Phe Phe Gln Leu Leu Met Lys Arg Lys Glu Leu

-25

-20

att ccc ttg gtg gtg ttc atg act gtg gcg gcg ggt gga gcc tca tct 278

Ile Pro Leu Val Val Phe Met Thr Val Ala Ala Gly Gly Ala Ser Ser

-15

-10

-5

ttc gct gtg tat tct ctt tgg aaa acc gat gtg atc ctt gat cga aaa 326

Phe Ala Val Tyr Ser Leu Trp Lys Thr Asp Val Ile Leu Asp Arg Lys

1

5

10

15

56

```
aaa aat cca gaa cct tgg gaa act gtg gac cct act gta cct caa aag      374
Lys Asn Pro Glu Pro Trp Glu Thr Val Asp Pro Thr Val Pro Gln Lys
      20              25              30
ctt ata aca atc aac caa caa tgg aaa ccc att gaa gag ttg caa aat      422
Leu Ile Thr Ile Asn Gln Gln Trp Lys Pro Ile Glu Glu Leu Gln Asn
      35              40              45
gtc caa agg gtg acc aaa tgacgagccc tcgcctcttt cttctgaaga      470
Val Gln Arg Val Thr Lys
      50
gtactctata aatctagtgg aaacatttct gcacaaacta gattctggac accagtgtgc      530
ggaaatgctt ctgctacatt tttagggttt gtctacattt tttgggtctt ggataaggaa      590
ttaaaggagt gcagcaataa ctgcactgtc caaaaaaaaa aaaaaa      636
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<210> 37

<211> 818

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 59..703

<220>

<221> sig_peptide

<222> 59..181

<223> Von Heijne matrix

score 6.80

seq LVSCLSQSSALS/QS

<220>

<221> polyA_signal

<222> 783..788

<220>

<221> polyA_site

<222> 804..818

<400> 37

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gacatcttga gctgaagcag ggttttgagc cactgctgct gctgctgcca ttgtcacc      58
atg gtc tca gct ctg cgg gga gca ccc ctg atc agg gtg cac tca agc      106
Met Val Ser Ala Leu Arg Gly Ala Pro Leu Ile Arg Val His Ser Ser
      -40              -35              -30
```

cct gtt tct tct cct tct gtg agt gga cca cgg agg ctg gtg agc tgc 154
 Pro Val Ser Ser Pro Ser Val Ser Gly Pro Arg Arg Leu Val Ser Cys
 -25 -20 -15 -10
 ctg tca tcc caa agc tca gct ctg agc cag agt ggt ggt ggc tcc acc 202
 Leu Ser Ser Gln Ser Ser Ala Leu Ser Gln Ser Gly Gly Gly Ser Thr
 -5 1 5
 tct gcc gcc ggc ata gaa gcc agg agc agg gct ctc aga agg cgg tgg 250
 Ser Ala Ala Gly Ile Glu Ala Arg Ser Arg Ala Leu Arg Arg Arg Trp
 10 15 20
 tgc cca gct ggg atc atg ttg ttg gcc ctg gtc tgt ctg ctc agc tgc 298
 Cys Pro Ala Gly Ile Met Leu Leu Ala Leu Val Cys Leu Leu Ser Cys
 25 30 35
 ctg cta ccc tcc agt gag gcc aag ctc tac ggt cgt tgt gaa ctg gcc 346
 Leu Leu Pro Ser Ser Glu Ala Lys Leu Tyr Gly Arg Cys Glu Leu Ala
 40 45 50 55
 aga gtg cta cat gac ttc ggg ctg gac gga tac cgg gga tac agc ctg 394
 Arg Val Leu His Asp Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu
 60 65 70
 gct gac tgg gtc tgc ctt gct tat ttc aca agc ggt ttc aac gca gct 442
 Ala Asp Trp Val Cys Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala
 75 80 85
 gct ttg gac tac gag gct gat ggg agc acc aac aac ggg atc ttc cag 490
 Ala Leu Asp Tyr Glu Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln
 90 95 100
 atc aac agc cgg agg tgg tgc agc aac ctc acc ccg aac gtc ccc aac 538
 Ile Asn Ser Arg Arg Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn
 105 110 115
 gtg tgc cgg atg tac tgc tca gat ttg ttg aat cct aat ctc aag gat 586
 Val Cys Arg Met Tyr Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp
 120 125 130 135
 acc gtt atc tgt gcc atg aag ata acc caa gag cct cag ggt ctg ggt 634
 Thr Val Ile Cys Ala Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly
 140 145 150
 tac tgg gag gcc tgg agg cat cac tgc cag gga aaa gac ctc act gaa 682
 Tyr Trp Glu Ala Trp Arg His His Cys Gln Gly Lys Asp Leu Thr Glu
 155 160 165
 tgg gtg gat ggc tgt gac ttc taggatggac ggaaccatgc acagcaggct 733
 Trp Val Asp Gly Cys Asp Phe
 170
 gggaaatgtg gtttggttcc tgacctaggc ttgggaagac aagccagcga ataaaggatg 793
 gttgaacgtg aaaaaaaaaa aaaaaa 818

<210> 38

<211> 1888

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 139..1389

<220>

<221> sig_peptide

<222> 139..198

<223> Von Heijne matrix

score 5.00

seq HLLAGFCVWVVLG/WV

<220>

<221> polyA_signal

<222> 1854..1859

<220>

<221> polyA_site

<222> 1873..1888

<400> 38

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ccccccagc tggaaccaag aaggttgtgt ccccttctct ctgggtgtcc ttgtctctctg      60
ctatcagggc acagtcctca ggaagtgttcg gggagaatag gagccagaac ctgagccctt      120
aagccattcc cctcacca atg atg ggg tcc cca gtg agt cat ctg ctg gcc      171
                Met Met Gly Ser Pro Val Ser His Leu Leu Ala
                -20                -15                -10
ggc ttc tgt gtg tgg gtc gtc ttg ggc tgg gta ggg ggc tca gtc ccc      219
Gly Phe Cys Val Trp Val Val Leu Gly Trp Val Gly Gly Ser Val Pro
                -5                1                5
aac ctg ggc cct gct gag cag gag cag aac cat tac ctg gcc cag ctg      267
Asn Leu Gly Pro Ala Glu Gln Glu Gln Asn His Tyr Leu Ala Gln Leu
                10                15                20
ttt ggc ctg tac ggc gag aat ggg acg ctg act gca ggg ggc ttg gcg      315
Phe Gly Leu Tyr Gly Glu Asn Gly Thr Leu Thr Ala Gly Gly Leu Ala
                25                30                35
cgg ctt ctc cac agc ctg ggg cta ggc cga gtt cag ggg ctt cgc ctg      363
Arg Leu Leu His Ser Leu Gly Leu Gly Arg Val Gln Gly Leu Arg Leu
                40                45                50                55

```

59

gga cag cat ggg cct ctg act gga cgg gct gca tcc cca gct gca gac	411
Gly Gln His Gly Pro Leu Thr Gly Arg Ala Ala Ser Pro Ala Ala Asp	
60 65 70	
aat tcc aca cac agg cca cag aac cct gag ctg agt gtg gat gtc tgg	459
Asn Ser Thr His Arg Pro Gln Asn Pro Glu Leu Ser Val Asp Val Trp	
75 80 85	
gca ggg atg cct ctg ggt ccc tca ggg tgg ggt gac ctg gaa gag tca	507
Ala Gly Met Pro Leu Gly Pro Ser Gly Trp Gly Asp Leu Glu Glu Ser	
90 95 100	
aag gcc cct cac cta ccc cgt ggg cca gcc ccc tgg ggc ctg gac ctc	555
Lys Ala Pro His Leu Pro Arg Gly Pro Ala Pro Ser Gly Leu Asp Leu	
105 110 115	
ctt cac agg ctt ctg ttg ctg gac cac tca ttg gct gac cac ctg aat	603
Leu His Arg Leu Leu Leu Leu Asp His Ser Leu Ala Asp His Leu Asn	
120 125 130 135	
gag gat tgt ctg aac ggc tcc cag ctg ctg gtc aat ttt ggc ttg agc	651
Glu Asp Cys Leu Asn Gly Ser Gln Leu Leu Val Asn Phe Gly Leu Ser	
140 145 150	
ccc gct gct cct ctg acc cct cgt cag ttt gct ctg ctg tgc cca gcc	699
Pro Ala Ala Pro Leu Thr Pro Arg Gln Phe Ala Leu Leu Cys Pro Ala	
155 160 165	
ctg ctt tat cag atc gac agc cgc gtc tgc atc ggc gct ccg gcc cct	747
Leu Leu Tyr Gln Ile Asp Ser Arg Val Cys Ile Gly Ala Pro Ala Pro	
170 175 180	
gca ccc cca ggg gat cta cta tct gcc ctg ctt cag agt gcc ctg gca	795
Ala Pro Pro Gly Asp Leu Leu Ser Ala Leu Leu Gln Ser Ala Leu Ala	
185 190 195	
gtc ctg ttg ctc agc ctc cct tct ccc cta tcc ctg ctg ctg ctg cgg	843
Val Leu Leu Leu Ser Leu Pro Ser Pro Leu Ser Leu Leu Leu Leu Arg	
200 205 210 215	
ctc ctg gga cct cgt cta cta cgg ccc ttg ctg ggc ttc ctg ggg gcc	891
Leu Leu Gly Pro Arg Leu Leu Arg Pro Leu Leu Gly Phe Leu Gly Ala	
220 225 230	
ctg gcg gtg ggc act ctt tgt ggg gat gca ctg cta cat ctg cta ccg	939
Leu Ala Val Gly Thr Leu Cys Gly Asp Ala Leu Leu His Leu Leu Pro	
235 240 245	
cat gca caa gaa ggg cgg cac gca gga cct ggc gga cta cca gag aag	987
His Ala Gln Glu Gly Arg His Ala Gly Pro Gly Gly Leu Pro Glu Lys	
250 255 260	
gac ctg ggc ccg ggg ctg tca gtg ctc gga ggc ctc ttc ctg ctc ttt	1035
Asp Leu Gly Pro Gly Leu Ser Val Leu Gly Gly Leu Phe Leu Leu Phe	
265 270 275	

60

```

gtg ctg gag aac atg ctg ggg ctt ttg cgg cac cga ggg ctc agg cca      1083
Val Leu Glu Asn Met Leu Gly Leu Leu Arg His Arg Gly Leu Arg Pro
280                285                290                295
aga tgc tgc agg cga aaa cga agg aat ctc gaa aca cgc aac ttg gat      1131
Arg Cys Cys Arg Arg Lys Arg Arg Asn Leu Glu Thr Arg Asn Leu Asp
300                305                310
ccg gag aat ggc agt ggg atg gcc ctt cag ccc cta cag gca gct cca      1179
Pro Glu Asn Gly Ser Gly Met Ala Leu Gln Pro Leu Gln Ala Ala Pro
315                320                325
gag cca ggg gct cag ggc cag agg gag aag aac agc cag cac cca cca      1227
Glu Pro Gly Ala Gln Gly Gln Arg Glu Lys Asn Ser Gln His Pro Pro
330                335                340
gct ctg gcc cct cct ggg cac caa ggc cac agt cat ggg cac cag ggt      1275
Ala Leu Ala Pro Pro Gly His Gln Gly His Ser His Gly His Gln Gly
345                350                355
ggc act gat atc acg tgg atg gtc ctc ctg gga gat ggt cta cac aac      1323
Gly Thr Asp Ile Thr Trp Met Val Leu Leu Gly Asp Gly Leu His Asn
360                365                370                375
ctc act gat ggg ctg gcc ata ggt gct gcc ttc tct gat ggc ttc tcc      1371
Leu Thr Asp Gly Leu Ala Ile Gly Ala Ala Phe Ser Asp Gly Phe Ser
380                385                390
gcg gcc tca gta cca cct tagcggtctt ctgccatgag ctgccccacg      1419
Ala Ala Ser Val Pro Pro
395
aactgggtga ctttgccatg ctgctccagt cagggtgtgc ctttcggcgg ctgctgctgc      1479
tgagcctcgt gtctggagcc ctgggattgg ggggtgcagt cctgggggtg gggctcagcc      1539
tgggccctgt cccctcact ccctgggtgt ttgggggtcac tgctggggtc ttcctctatg      1599
tggcccttgt ggacatgcta ccagccctgc ttcgtcctcc ggagccccctg cctacgcccc      1659
atgtgctcct gcaggggctg gggctgctgc tggggggcgg cctcatgctt gccataaccc      1719
tgctggagga gcggctactg ccctgacca ctgagggctg atggggccag tggaaagggg      1779
tcgggttccc cttccttccc cccaaccaca ggaatggagg cgggacacag ggccagtagg      1839
agcaatagga ttttaataaa cagaacccat cccaaaaaaa aaaaaaaaaa      1888

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<210> 39

<211> 1894

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 21..1118

<220>

<221> sig_peptide

<222> 21..89

<223> Von Heijne matrix

score 10.80

seq ALALLSAFSATQA/RK

<220>

<221> polyA_signal

<222> 1858..1863

<220>

<221> polyA_site

<222> 1879..1894

<220>

<221> misc_feature

<222> 1695

<223> n=a, g, c or t

<400> 39

agacgtgagc agagcagata atg gca agc atg gct gcc gtg ctc acc tgg gct 53
 Met Ala Ser Met Ala Ala Val Leu Thr Trp Ala

-20

-15

ctg gct ctt ctt tca gcg ttt tcg gcc acc cag gca cgg aaa ggc ttc 101
 Leu Ala Leu Leu Ser Ala Phe Ser Ala Thr Gln Ala Arg Lys Gly Phe

-10

-5

1

tgg gac tac ttc agc cag acc agc ggg gac aaa ggc agg gtg gag cag 149
 Trp Asp Tyr Phe Ser Gln Thr Ser Gly Asp Lys Gly Arg Val Glu Gln

5

10

15

20

atc cat cag cag aag atg gct cgc gag ccc gcg acc ctg aaa gac agc 197
 Ile His Gln Gln Lys Met Ala Arg Glu Pro Ala Thr Leu Lys Asp Ser

25

30

35

ctt gag caa gac ctc aac aat atg aac aag ttc ctg gaa aag ctg agg 245
 Leu Glu Gln Asp Leu Asn Asn Met Asn Lys Phe Leu Glu Lys Leu Arg

40

45

50

cct ctg agt ggg agc gag gct cct cgg ctc cca cag gac ccg gtg ggc 293
 Pro Leu Ser Gly Ser Glu Ala Pro Arg Leu Pro Gln Asp Pro Val Gly

55

60

65

atg cgg cgg cag ctg cag gag gag ttg gag gag gtg aag gct cgc ctc 341
 Met Arg Arg Gln Leu Gln Glu Glu Leu Glu Glu Val Lys Ala Arg Leu

70

75

80

cag ccc tac atg gca gag gcg cac gag ctg gtg ggc tgg aat ttg gag 389
 Gln Pro Tyr Met Ala Glu Ala His Glu Leu Val Gly Trp Asn Leu Glu
 85 90 95 100
 ggc ttg cgg cag caa ctg aag ccc tac acg atg gat ctg atg gag cag 437
 Gly Leu Arg Gln Gln Leu Lys Pro Tyr Thr Met Asp Leu Met Glu Gln
 105 110 115
 gtg gcc ctg cgc gtg cag gag ctg cag gag cag ttg cgc gtg gtg ggg 485
 Val Ala Leu Arg Val Gln Glu Leu Gln Glu Gln Leu Arg Val Val Gly
 120 125 130
 gaa gac acc aag gcc cag ttg ctg ggg ggc gtg gac gag gct tgg gct 533
 Glu Asp Thr Lys Ala Gln Leu Leu Gly Gly Val Asp Glu Ala Trp Ala
 135 140 145
 ttg ctg cag gga ctg cag agc cgc gtg gtg cac cac acc ggc cgc ttc 581
 Leu Leu Gln Gly Leu Gln Ser Arg Val Val His His Thr Gly Arg Phe
 150 155 160
 aaa gag ctc ttc cac cca tac gcc gag agc ctg gtg agc ggc atc ggg 629
 Lys Glu Leu Phe His Pro Tyr Ala Glu Ser Leu Val Ser Gly Ile Gly
 165 170 175 180
 cgc cac gtg cag gag ctg cac cgc agt gtg gct ccg cac gcc ccc gcc 677
 Arg His Val Gln Glu Leu His Arg Ser Val Ala Pro His Ala Pro Ala
 185 190 195
 agc ccc gcg cgc ctc agt cgc tgc gtg cag gtg ctc tcc cgg aag ctc 725
 Ser Pro Ala Arg Leu Ser Arg Cys Val Gln Val Leu Ser Arg Lys Leu
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 acg ctc aag gcc aag gcc ctg cac gca cgc atc cag cag aac ctg gac 773
 Thr Leu Lys Ala Lys Ala Leu His Ala Arg Ile Gln Gln Asn Leu Asp
 215 220 225
 cag ctg cgc gaa gag ctc agc aga gcc ttt gca ggc act ggg act gag 821
 Gln Leu Arg Glu Glu Leu Ser Arg Ala Phe Ala Gly Thr Gly Thr Glu
 230 235 240
 gaa ggg gcc ggc ccg gac ccc cag atg ctc tcc gag gag gtg cgc cag 869
 Glu Gly Ala Gly Pro Asp Pro Gln Met Leu Ser Glu Glu Val Arg Gln
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 cga ctt cag gct ttc cgc cag gac acc tac ctg cag ata gct gcc ttc 917
 Arg Leu Gln Ala Phe Arg Gln Asp Thr Tyr Leu Gln Ile Ala Ala Phe
 265 270 275
 act cgc gcc atc gac cag gag act gag gag gtc cag cag cag ctg gcg 965
 Thr Arg Ala Ile Asp Gln Glu Thr Glu Glu Val Gln Gln Gln Leu Ala
 280 285 290
 cca cct cca cca ggc cac agt gcc ttc gcc cca gag ttt caa caa aca 1013
 Pro Pro Pro Pro Gly His Ser Ala Phe Ala Pro Glu Phe Gln Gln Thr
 295 300 305

gac agt ggc aag gtt ctg agc aag ctg cag gcc cgt ctg gat gac ctg 1061
Asp Ser Gly Lys Val Leu Ser Lys Leu Gln Ala Arg Leu Asp Asp Leu
310 315 320
tgg gaa gac atc act cac agc ctt cat gac cag ggc cac agc cat ctg 1109
Trp Glu Asp Ile Thr His Ser Leu His Asp Gln Gly His Ser His Leu
325 330 335 340
ggg gac ccc tgaggatcta cctgcccagg cccattccca gtccttgtc 1158
Gly Asp Pro
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aaaaaaaa aaaaaa 1894

<210> 40

<211> 1913

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 143..592

<220>

<221> sig_peptide

<222> 143..277

<223> Von Heijne matrix

score 5.90

seq VLVDLAILGQAYA/FA

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<222> 1877..1882

<220>

<221> polyA_site

<222> 1899..1913

<400> 40

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cagagacggc aggttcatca ag atg gtg ctc atg tgg acc agt ggt gac gcc 172
Met Val Leu Met Trp Thr Ser Gly Asp Ala
-45 -40

ttc aag acg gcc tac ttc ctg ctg aag ggt gcc cct ctg cag ttc tcc 220
Phe Lys Thr Ala Tyr Phe Leu Leu Lys Gly Ala Pro Leu Gln Phe Ser
-35 -30 -25 -20

gtg tgc ggc ctg ctg cag gtg ctg gtg gac ctg gcc atc ctg ggg cag 268
Val Cys Gly Leu Leu Gln Val Leu Val Asp Leu Ala Ile Leu Gly Gln
-15 -10 -5

gcc tac gcc ttc gcc cca ccc cca gaa gcc ggc gcc cca cgc cgt gca 316
Ala Tyr Ala Phe Ala Pro Pro Pro Glu Ala Gly Ala Pro Arg Arg Ala
1 5 10

ccc cac tgg cac caa ggc cct ctg aca gtg ggg agg acg agg atg tgg 364
Pro His Trp His Gln Gly Pro Leu Thr Val Gly Arg Thr Arg Met Trp
15 20 25

gac cgc cag ccg cgg gca ctg gtg ggc cct gac ctc ccc gcg ggg agg 412
Asp Arg Gln Pro Arg Ala Leu Val Gly Pro Asp Leu Pro Ala Gly Arg
30 35 40 45

gtg ggt gcc gtg gcc cct gca ggt gtg gca gag atg ggg cac ggg cat 460
Val Gly Ala Val Ala Pro Ala Gly Val Ala Glu Met Gly His Gly His
50 55 60

tgg ggt ctc cat cag cct ctg tgg ggt gtc tca ggg tgg gca gtg ggg 508
Trp Gly Leu His Gln Pro Leu Trp Gly Val Ser Gly Trp Ala Val Gly
65 70 75

gtg ggg ctg gga cgc tgt ttg tgc tca gcg ggg aca gcc agg gtt gat 556
Val Gly Leu Gly Arg Cys Leu Cys Ser Ala Gly Thr Ala Arg Val Asp
80 85 90

ctg gcc ccg agg gtt ttg gat gtt ttt agg atg aca taaaaagcaa 602
Leu Ala Pro Arg Val Leu Asp Val Phe Arg Met Thr
95 100 105

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ggcgacttgg aatcaataaaa ccatttgtgg atcctaataa aaaaaaaaaa a 1913
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<210> 41

<211> 1744

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 76..999

<220>

<221> sig_peptide

<222> 76..279

<223> Von Heijne matrix

score 5.10

seq LSLPVCTVSLVSS/VS

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<221> polyA_signal

<222> 1711..1716

<220>

<221> polyA_site

<222> 1729..1744

<220>

<221> misc_feature

<222> 336

<223> n=a, g, c or t

<400> 41

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cgccacacct tgttc atg gat ttt gtc gct gga gcc atc gga ggc gtc tgc      111
      Met Asp Phe Val Ala Gly Ala Ile Gly Gly Val Cys
                        -65                -60

ggt gtt gct gtg ggc tac ccc ctg gac acg gtg aag gtc agg atc cag      159
Gly Val Ala Val Gly Tyr Pro Leu Asp Thr Val Lys Val Arg Ile Gln
      -55                -50                -45

acg gag cca aag tac aca ggc atc tgg cac tgc gtc cgg gat acg tat      207
Thr Glu Pro Lys Tyr Thr Gly Ile Trp His Cys Val Arg Asp Thr Tyr.
      -40                -35                -30                -25

cac cga gag cgc gtg tgg ggc ttc tac cgg ggc ctc tcg ctg ccc gtg      255
His Arg Glu Arg Val Trp Gly Phe Tyr Arg Gly Leu Ser Leu Pro Val
                        -20                -15                -10

tgc acg gtg tcc ctg gta tct tcc gtg tct ttt ggc acc tac cgc cac      303
Cys Thr Val Ser Leu Val Ser Ser Val Ser Phe Gly Thr Tyr Arg His
      -5                1                5

tgc ctg gcg cac atc tgc cgg ctc cgg tac ggn aac cct gac gcc aag      351
Cys Leu Ala His Ile Cys Arg Leu Arg Tyr Gly Asn Pro Asp Ala Lys
      10                15                20

ccc acc aag gcc gac atc acg ctc tcg gga tgc gcc tcc ggc ctc gtc      399
Pro Thr Lys Ala Asp Ile Thr Leu Ser Gly Cys Ala Ser Gly Leu Val
      25                30                35                40

cgc gtg ttc ctg acg tcg ccc act gag gtg gcc aaa gtc cgc ttg cag      447
Arg Val Phe Leu Thr Ser Pro Thr Glu Val Ala Lys Val Arg Leu Gln
                        45                50                55

acg cag aca cag gcg cag aag cag cag cgg ctg ctt tcg gcc tcg ggg      495
Thr Gln Thr Gln Ala Gln Lys Gln Gln Arg Leu Leu Ser Ala Ser Gly
      60                65                70

ccg ttg gct gtg ccc ccc atg tgt cct gtg ccc cca gcc tgc cca gag      543
Pro Leu Ala Val Pro Pro Met Cys Pro Val Pro Pro Ala Cys Pro Glu
      75                80                85

ccc aag tac cgc ggg cca ctg cac tgc ctg gcc acg gta gcc cgt gag      591
Pro Lys Tyr Arg Gly Pro Leu His Cys Leu Ala Thr Val Ala Arg Glu
      90                95                100

gag ggg ctg tgc ggc ctc tac aag ggc agc tcg gcc ctg gtc tta cgg      639
Glu Gly Leu Cys Gly Leu Tyr Lys Gly Ser Ser Ala Leu Val Leu Arg

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105 110 115 120
 gac ggc cac tcc ttt gcc acc tac ttc ctt tcc tac gcg gtc ctc tgc 687
 Asp Gly His Ser Phe Ala Thr Tyr Phe Leu Ser Tyr Ala Val Leu Cys
 125 130 135
 gag tgg ctc agc ccc gct ggc cac agc cgg cca gat gtc ccg ggc gtg 735
 Glu Trp Leu Ser Pro Ala Gly His Ser Arg Pro Asp Val Pro Gly Val
 140 145 150
 ctg gtg gcc ggg ggc tgt gca gga gtc ctg gcc tgg gct gtg gcc acc 783
 Leu Val Ala Gly Gly Cys Ala Gly Val Leu Ala Trp Ala Val Ala Thr
 155 160 165
 ccc atg gac gtg atc aag tgc aga ctg cag gca gac ggg cag ggc cag 831
 Pro Met Asp Val Ile Lys Ser Arg Leu Gln Ala Asp Gly Gln Gly Gln
 170 175 180
 agg cgc tac cgg ggt ctc ctg cac tgt atg gtg acc agc gtt cga gag 879
 Arg Arg Tyr Arg Gly Leu Leu His Cys Met Val Thr Ser Val Arg Glu
 185 190 195 200
 gag gga ccc cgg gtc ctt ttc aag ggg ctg gta ctc aat tgc tgc cgc 927
 Glu Gly Pro Arg Val Leu Phe Lys Gly Leu Val Leu Asn Cys Cys Arg
 205 210 215
 gcc ttc cct gtc aac atg gtg gtc ttc gtc gcc tat gag gca gtg ctg 975
 Ala Phe Pro Val Asn Met Val Val Phe Val Ala Tyr Glu Ala Val Leu
 220 225 230
 agg ctc gcc cgg ggt ctg ctc aca tagccgggtcc ccacgcccag cggcccaccc 1029
 Arg Leu Ala Arg Gly Leu Leu Thr
 235 240
 accagcagct gctggagggtc gtagtggtctg gaggaggcaa ggggtagtgt ggctgggttc 1089
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 ttctcagga gccctcactc tgctgtgga cgctgcacct gccacttaaa gaccccaaag 1689
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<210> 42

<211> 946

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 123..464

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<221> sig_peptide

<222> 123..269

<223> Von Heijne matrix

score 4.90

seq PSLAAGLLFGSLA/GL

<220>

<221> polyA_signal

<222> 908..913

<220>

<221> polyA_site

<222> 931..946

<400> 42

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ga atg gag aag ccc ctc ttc cca tta gtg cct ttg cat tgg ttt ggc      167
    Met Glu Lys Pro Leu Phe Pro Leu Val Pro Leu His Trp Phe Gly
          -45                -40                -35
ttt ggc tac aca gca ctg gtt gtt tct ggt ggg atc gtt ggc tat gta      215
Phe Gly Tyr Thr Ala Leu Val Val Ser Gly Gly Ile Val Gly Tyr Val
          -30                -25                -20
aaa aca ggc agc gtg ccg tcc ctg gct gca ggg ctg ctc ttc ggc agt      263
Lys Thr Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser
          -15                -10                -5
cta gcc ggc ctg ggt gct tac cag ctg tat cag gat cca agg aac gtt      311
Leu Ala Gly Leu Gly Ala Tyr Gln Leu Tyr Gln Asp Pro Arg Asn Val
          1                5                10
tgg ggt ttc cta gcc gct aca tct gtt act ttt gtt ggt gtt atg gga      359
Trp Gly Phe Leu Ala Ala Thr Ser Val Thr Phe Val Gly Val Met Gly
          15                20                25                30
atg aga tcc tac tac tat gga aaa ttc atg cct gta ggt tta att gca      407
Met Arg Ser Tyr Tyr Tyr Gly Lys Phe Met Pro Val Gly Leu Ile Ala
          35                40                45
ggg gcc agt ttg ctg atg gcc gcc aaa gtt gga gtt cgt atg ttg atg      455

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Gly Ala Ser Leu Leu Met Ala Ala Lys Val Gly Val Arg Met Leu Met

50

55

60

aca tct gat tagcagaagt catgttccag cttggactca tgaaggatta

504

Thr Ser Asp

65

aaaatctgca tcttccacta ttttcaatgt attaagagaa ataagtcag cttttttgca

564

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624

tggtaccatt ataaccctac agaggtggtg agcatgtaac atgagcttat tgagaccatc

684

atagagatcg attcttgtat attgatttta tctctttctg tatctatagg taaatctcaa

744

gggtaaaatg ttaggtgttg acattgagaa ccctgaaacc ccattccctg ctcagaggaa

804

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924

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946

<210> 43

<211> 1622

<212> DNA

<213> Homo Sapiens

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<221> CDS

<222> 85..1230

<220>

<221> sig_peptide

<222> 85..129

<223> Von Heijne matrix

score 10.10

seq LLLPLALCILVLC/CG

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<221> polyA_signal

<222> 1589..1594

<220>

<221> polyA_site

<222> 1607..1622

<400> 43

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atcctgggcc ttgttctcca caga atg ggt ctg ctc ctt ccc ctg gca ctc

111

Met Gly Leu Leu Leu Pro Leu Ala Leu

	-15	-10	
tgc atc cta gtc ctg tgc tgc gga gca atg tct cca ccc cag ctg gcc			159
Cys Ile Leu Val Leu Cys Cys Gly Ala Met Ser Pro Pro Gln Leu Ala			
-5	1	5	10
ctc aac ccc tcg gct ctg ctc tcc cgg ggc tgc aat gac tca gat gtg			207
Leu Asn Pro Ser Ala Leu Leu Ser Arg Gly Cys Asn Asp Ser Asp Val			
15	20	25	
ctg gca gtt gca ggc ttt gcc ctg cgg gat att aac aaa gac aga aag			255
Leu Ala Val Ala Gly Phe Ala Leu Arg Asp Ile Asn Lys Asp Arg Lys			
30	35	40	
gat ggc tat gtg ctg aga ctc aac cga gtg aac gac gcc cag gaa tac			303
Asp Gly Tyr Val Leu Arg Leu Asn Arg Val Asn Asp Ala Gln Glu Tyr			
45	50	55	
aga cgg ggt ggc ctg gga tct ctg ttc tat ctt aca ctg gat gtg cta			351
Arg Arg Gly Gly Leu Gly Ser Leu Phe Tyr Leu Thr Leu Asp Val Leu			
60	65	70	
gag act gac tgc cat gtg ctc aga aag aag gca tgg caa gac tgt gga			399
Glu Thr Asp Cys His Val Leu Arg Lys Lys Ala Trp Gln Asp Cys Gly			
75	80	85	90
atg agg ata ttt ttt gaa tca gtt tat ggt caa tgc aaa gca ata ttt			447
Met Arg Ile Phe Phe Glu Ser Val Tyr Gly Gln Cys Lys Ala Ile Phe			
95	100	105	
tat atg aac aac cca agt aga gtt ctc tat tta gct gct tat aac tgt			495
Tyr Met Asn Asn Pro Ser Arg Val Leu Tyr Leu Ala Ala Tyr Asn Cys			
110	115	120	
act ctt cgc cca gtt tca aaa aaa aag att tac atg acg tgc cct gac			543
Thr Leu Arg Pro Val Ser Lys Lys Lys Ile Tyr Met Thr Cys Pro Asp			
125	130	135	
tgc cca agc tcc ata ccc act gac tct tcc aat cac caa gtg ctg gag			591
Cys Pro Ser Ser Ile Pro Thr Asp Ser Ser Asn His Gln Val Leu Glu			
140	145	150	
gct gcc acc gag tct ctt gcg aaa tac aac aat gag aac aca tcc aag			639
Ala Ala Thr Glu Ser Leu Ala Lys Tyr Asn Asn Glu Asn Thr Ser Lys			
155	160	165	170
cag tat tct ctc ttc aaa gtc acc agg gct tct agc cag tgg gtg gtc			687
Gln Tyr Ser Leu Phe Lys Val Thr Arg Ala Ser Ser Gln Trp Val Val			
175	180	185	
ggc cct tct tac ttt gtg gaa tac tta att aaa gaa tca cca tgt act			735
Gly Pro Ser Tyr Phe Val Glu Tyr Leu Ile Lys Glu Ser Pro Cys Thr			
190	195	200	
aaa tcc cag gcc agc agc tgt tca ctt cag tcc tcc gac tct gtg cct			783
Lys Ser Gln Ala Ser Ser Cys Ser Leu Gln Ser Ser Asp Ser Val Pro			

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      205      210      215
gtt ggt ctt tgc aaa ggt tct ctg act cga aca cac tgg gaa aag ttt      831
Val Gly Leu Cys Lys Gly Ser Leu Thr Arg Thr His Trp Glu Lys Phe

      220      225      230
gtc tct gtg act tgt gac ttc ttt gaa tca cag gct cca gcc act gga      879
Val Ser Val Thr Cys Asp Phe Phe Glu Ser Gln Ala Pro Ala Thr Gly

      235      240      245      250
agt gaa aac tct gct gtt aac cag aaa cct aca aac ctt ccc aag gtg      927
Ser Glu Asn Ser Ala Val Asn Gln Lys Pro Thr Asn Leu Pro Lys Val

      255      260      265
gaa gaa tcc cag cag aaa aac acc ccc cca aca gac tcc ccc tcc aaa      975
Glu Glu Ser Gln Gln Lys Asn Thr Pro Pro Thr Asp Ser Pro Ser Lys

      270      275      280
gct ggg cca aga gga tct gtc caa tat ctt cct gac ttg gat gat aaa      1023
Ala Gly Pro Arg Gly Ser Val Gln Tyr Leu Pro Asp Leu Asp Asp Lys

      285      290      295
aat tcc cag gaa aag ggc cct cag gag gcc ttt cct gtg cat ctg gac      1071
Asn Ser Gln Glu Lys Gly Pro Gln Glu Ala Phe Pro Val His Leu Asp

      300      305      310
cta acc acg aat ccc cag gga gaa acc ctg gat att tcc ttc ctc ttc      1119
Leu Thr Thr Asn Pro Gln Gly Glu Thr Leu Asp Ile Ser Phe Leu Phe

      315      320      325      330
ctg gag cct atg gag gag aag ctg gtg gtc ctg cct ttc ccc aaa gaa      1167
Leu Glu Pro Met Glu Glu Lys Leu Val Val Leu Pro Phe Pro Lys Glu

      335      340      345
aaa gca cgc act gct gag tgc cca ggg cca gcc cag aat gcc agc cct      1215
Lys Ala Arg Thr Ala Glu Cys Pro Gly Pro Ala Gln Asn Ala Ser Pro

      350      355      360
ctt gtc ctt ccg cca tgagaatcac acagagtctt ctgtaggggt atgggtgcgc      1270
Leu Val Leu Pro Pro

      365
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gctgcatcac ctctaaact gagcagtctc ataccatgga gagatgcctc tcttatgtct      1510
tcagccactc acttataaag atacttatct ttccagcagt atatatgtgc tgaaatctca      1570
gcatgaaagc attgcatgag taaagatact ttccctaaaa aaaaaaaaaa aa      1622

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<210> 44

<211> 715

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 29..664

<220>

<221> sig_peptide

<222> 29..619

<223> Von Heijne matrix

score 4.80

seq SFFGASFLMGSLG/GM

<220>

<221> polyA_signal

<222> 657..662

<220>

<221> polyA_site

<222> 699..715

<220>

<221> misc_feature

<222> 295,357

<223> n=a, g, c or t

<220>

<221> unsure

<222> -88

<223> Xaa = Ala,Asp,Gly,Val

<220>

<221> unsure

<222> -109

<223> Xaa = Asp,Glu

<400> 44

cttttcctgc ctctgattcc gggctgtc atg gcg acc ccc aac aat ctg acc 52

Met Ala Thr Pro Asn Asn Leu Thr

-195

-190

ccc acc aac tgc agc tgg tgg ccc atc tcc gcg ctg gag agc gat gcg 100

Pro Thr Asn Cys Ser Trp Trp Pro Ile Ser Ala Leu Glu Ser Asp Ala

-185

-180

-175

```

gcc aag cca gcg gag gcc ccc gac gct ccc gag gcg gcc agc ccc gcc      148
Ala Lys Pro Ala Glu Ala Pro Asp Ala Pro Glu Ala Ala Ser Pro Ala
      -170                -165                -160
cat tgg ccc agg gag agc ctg gtt ctg tac cac tgg acc cag tcc ttc      196
His Trp Pro Arg Glu Ser Leu Val Leu Tyr His Trp Thr Gln Ser Phe
      -155                -150                -145
agc tcg cag aag gcc aag atc ttg gag cat gat gat gtg agc tac ctg      244
Ser Ser Gln Lys Ala Lys Ile Leu Glu His Asp Asp Val Ser Tyr Leu
      -140                -135                -130
aag aag atc ctc ggg gaa ctg gcc atg gtg ctg gac cag att gag gcg      292
Lys Lys Ile Leu Gly Glu Leu Ala Met Val Leu Asp Gln Ile Glu Ala
      -125                -120                -115                -110
gan ctg gag aag agg aag ctg gag aac gag ggg cag aaa tgc gag ctg      340
Xaa Leu Glu Lys Arg Lys Leu Glu Asn Glu Gly Gln Lys Cys Glu Leu
      -105                -100                -95
tgg ctc tgt ggc tgt gnc ttc acc ctc gct gat gtc ctc ctg gga gcc      388
Trp Leu Cys Gly Cys Xaa Phe Thr Leu Ala Asp Val Leu Leu Gly Ala
      -90                -85                -80
acc ctg cac cgc ctc aag ttc ctg gga ctg tcc aag aaa tac tgg gaa      436
Thr Leu His Arg Leu Lys Phe Leu Gly Leu Ser Lys Lys Tyr Trp Glu
      -75                -70                -65
gat ggc agc cgg ccc aac ctg cag tcc ttc ttt gag agg gtc cag aga      484
Asp Gly Ser Arg Pro Asn Leu Gln Ser Phe Phe Glu Arg Val Gln Arg
      -60                -55                -50
cgc ttt gcc ttc cgg aaa gtc ctg ggt gac atc cac acc acc ctg ctg      532
Arg Phe Ala Phe Arg Lys Val Leu Gly Asp Ile His Thr Thr Leu Leu
      -45                -40                -35                -30
tcg gcc gtc atc ccc aat gct ttc cgg ctg gtc aag agg aaa ccc cca      580
Ser Ala Val Ile Pro Asn Ala Phe Arg Leu Val Lys Arg Lys Pro Pro
      -25                -20                -15
tcc ttc ttc ggg gcg tcc ttc ctc atg ggc tcc ctg ggt ggg atg ggc      628
Ser Phe Phe Gly Ala Ser Phe Leu Met Gly Ser Leu Gly Gly Met Gly
      -10                -5                1
tac ttt gcc tac tgg tac ctc aag aaa aaa tac atc tagggccagg      674
Tyr Phe Ala Tyr Trp Tyr Leu Lys Lys Lys Tyr Ile
      5                10                15
cctggggcctt ggtgtctgac tgccaaaaaa aaaaaaaaaa a      715

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<210> 45

<211> 1549

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 18..878

<220>

<221> sig_peptide

<222> 18..95

<223> Von Heijne matrix

score 6.30

seq GVGLVTLLGLAVG/SY

<220>

<221> polyA_signal

<222> 1500..1505

<220>

<221> polyA_site

<222> 1533..1549

<220>

<221> misc_feature

<222> 944

<223> n=a, g, c or t

<400> 45

ggaaaaggcg ctccgtc atg ggg atc cag acg agc ccc gtc ctg ctg gcc 50

Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala

-25

-20

tcc ctg ggg gtg ggg ctg gtc act ctg ctc ggc ctg gct gtg ggc tcc 98

Ser Leu Gly Val Gly Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser

-15 -10 -5 1

tac ttg gtt cgg agg tcc cgc cgg cct cag gtc act ctc ctg gac ccc 146

Tyr Leu Val Arg Arg Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro

5

10

15

aat gaa aag tac ctg cta cga ctg cta gac aag acg ctc tct gca cgg 194

Asn Glu Lys Tyr Leu Leu Arg Leu Leu Asp Lys Thr Leu Ser Ala Arg

20

25

30

tcc cca ggc aaa cat atc tac ctc tcc acc cga att gat ggc agc ctg 242

Ser Pro Gly Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu

35

40

45

gtc atc agg cca tac act cct gtc acc agt gat gag gat caa ggc tat 290

97

```

ttttcagtta catctagagc tgaaatctgg atagtacctg caggaacaat attcctgtag 1038
ccatggaaga gggccaaggc tcagtcactc ctgggatggc ctccctaaac tccccgtggc 1098
aacagggtcca ggagaggccc atggagcagt ctcttccatg gagtaagaag gaagggagca 1158
tgtacgcttg gtccaagatt ggctagtacc ttgatagcat cttactctca cttcttttgt 1218
gtctgtgatg aaaggaacag tctgtgcaat gggttttact taaacttcac tgttcaacct 1278
atgagcaaat ctgtatgtgt gagtataagt tgagcatagc atacttccag aggtggctctt 1338
atgggatggg caagaaagga ggaaatgatt tcttcagatc tcaaaggagt ctgaaatata 1398
atatctctgt gtgtgtctct ctccagccct gccagggcta gagggaaaca gctactgata 1458
atcgaaaact gctgtttgtg gcaggaaccc ctggctgtgc aaataaatgg ggctgaggcc 1518
cctgtgtgat attcaaaaaa aaaaaaaaaa a 1549

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<210> 46

<211> 1328

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 73..1008

<220>

<221> sig_peptide

<222> 73..147

<223> Von Heijne matrix

score 14.10

seq LLLLLLLTLLAFA/GY

<220>

<221> polyA_signal

<222> 1286..1291

<220>

<221> polyA_site

<222> 1312..1328

<400> 46

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actgcgcgga tcggcgctccg cagcggggcgg ctgctgagct gccttgaggt gcagtgttgg 60
ggatccagag cc atg tcg gac ctg cta cta ctg ggc ctg att ggg ggc ctg 111
Met Ser Asp Leu Leu Leu Leu Gly Leu Ile Gly Gly Leu
-25 -20 -15
act ctc tta ctg ctg ctg acg ctg cta gcc ttt gcc ggg tac tca ggg 159
Thr Leu Leu Leu Leu Leu Thr Leu Leu Ala Phe Ala Gly Tyr Ser Gly

```

-10	-5	1	
cta ctg gct ggg gtg gaa gtg agt gct ggg tca ccc ccc atc cgc aac	207		
Leu Leu Ala Gly Val Glu Val Ser Ala Gly Ser Pro Pro Ile Arg Asn			
5 10 15 20			
gtc act gtg gcc tac aag ttc cac atg ggg ctc tat ggt gag act ggg	255		
Val Thr Val Ala Tyr Lys Phe His Met Gly Leu Tyr Gly Glu Thr Gly			
25 30 35			
cgg ctt ttc act gag agc tgc atc tct ccc aag ctc cgc tcc atc gct	303		
Arg Leu Phe Thr Glu Ser Cys Ile Ser Pro Lys Leu Arg Ser Ile Ala			
40 45 50			
gtc tac tat gac aac ccc cac atg gtg ccc cct gat aag tgc cga tgt	351		
Val Tyr Tyr Asp Asn Pro His Met Val Pro Pro Asp Lys Cys Arg Cys			
55 60 65			
gcc gtg ggc agc atc ctg agt gaa ggt gag gaa tcg ccc tcc cct gag	399		
Ala Val Gly Ser Ile Leu Ser Glu Gly Glu Glu Ser Pro Ser Pro Glu			
70 75 80			
ctc atc gac ctc tac cag aaa ttt ggc ttc aag gtg ttc tcc ttc ccg	447		
Leu Ile Asp Leu Tyr Gln Lys Phe Gly Phe Lys Val Phe Ser Phe Pro			
85 90 95 100			
gca ccc agc cat gtg gtg aca gcc acc ttc ccc tac acc acc att ctg	495		
Ala Pro Ser His Val Val Thr Ala Thr Phe Pro Tyr Thr Thr Ile Leu			
105 110 115			
tcc atc tgg ctg gct acc cgc cgt gtc cat cct gcc ttg gac acc tac	543		
Ser Ile Trp Leu Ala Thr Arg Arg Val His Pro Ala Leu Asp Thr Tyr			
120 125 130			
atc aag gag cgg aag ctg tgt gcc tat cct cgg ctg gag atc tac cag	591		
Ile Lys Glu Arg Lys Leu Cys Ala Tyr Pro Arg Leu Glu Ile Tyr Gln			
135 140 145			
gaa gac cag atc cat ttc atg tgc cca ctg gca cgg cag gga gac ttc	639		
Glu Asp Gln Ile His Phe Met Cys Pro Leu Ala Arg Gln Gly Asp Phe			
150 155 160			
tat gtg cct gag atg aag gag aca gag tgg aaa tgg cgg ggg ctt gtg	687		
Tyr Val Pro Glu Met Lys Glu Thr Glu Trp Lys Trp Arg Gly Leu Val			
165 170 175 180			
gag gcc att gac acc cag gtg gat gcc aca gga gct gac aca atg agt	735		
Glu Ala Ile Asp Thr Gln Val Asp Gly Thr Gly Ala Asp Thr Met Ser			
185 190 195			
gac acg agt tct gta agc ttg gaa gtg agc cct ggc agc cgg gag act	783		
Asp Thr Ser Ser Val Ser Leu Glu Val Ser Pro Gly Ser Arg Glu Thr			
200 205 210			
tca gct gcc aca ctg tca cct ggg gcg agc agc cgt ggc tgg gat gac	831		
Ser Ala Ala Thr Leu Ser Pro Gly Ala Ser Ser Arg Gly Trp Asp Asp			


```

      215              220              225
ggt gac acc cgc agc gag cac agc tac agc gag tca ggt gcc agc ggc      879
Gly Asp Thr Arg Ser Glu His Ser Tyr Ser Glu Ser Gly Ala Ser Gly
      230              235              240
tcc tct ttt gag gag ctg gac ttg gag ggc gag ggg ccc tta ggg gag      927
Ser Ser Phe Glu Glu Leu Asp Leu Glu Gly Glu Gly Pro Leu Gly Glu
      245              250              255              260
tca cgg ctg gac cct ggg act gag ccc ctg ggg act acc aag tgg ctc      975
Ser Arg Leu Asp Pro Gly Thr Glu Pro Leu Gly Thr Thr Lys Trp Leu
      265              270              275
tgg gag ccc act gcc cct gag aag ggc aag gag taaccocatgg cctgcaccct 1028
Trp Glu Pro Thr Ala Pro Glu Lys Gly Lys Glu
      280              285
cctgcagtgc agttgctgag gaactgagca gactctccag cagactctcc agccctcttc 1088
ctccttcttc tgggggagga ggggttctctg agggacctga cttcccttgc tccaggcctc 1148
ttgctaagcc ttctcctcac tgccctttag gctcccaggg ccagaggagc cagggactat 1208
tttctgcacc agcccccagg gctgccaccc ctgttgtgtc tttttttcag actcacagtg 1268
gagcttccag gaccacagaat aaagccaatg atttacttgt ttcaaaaaaa aaaaaaaaaa 1328
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<210> 47

<211> 1515

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 165..842

<220>

<221> sig_peptide

<222> 165..251

<223> Von Heijne matrix

score 7.00

seq LASFAALVLVCRO/RV

<220>

<221> polyA_signal

<222> 1474..1479

<220>

<221> polyA_site

<222> 1500..1515

<400> 47

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agtcgcggga tgcgcccgga agccacagcc tgaggccctc aggtctctgc aggtgtcgtg      60
gaggaaacct gacactgcca tcctcttccc caatttgcca cttccagcag ctttagccca      120
tgaggaggat gtgaccggga ctgagtcagg agccctctgg aagc atg gag act gtg      176
                               Met Glu Thr Val
gtg att gtt gcc ata ggt gtg ctg gcc acc atc ttt ctg gct tcg ttt      224
Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe Leu Ala Ser Phe
-25                -20                -15                -10
gca gcc ttg gtg ctg gtt tgc agg cag cgc tac tgc cgg ccg cga gac      272
Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys Arg Pro Arg Asp
                               -5                1                5
ctg ctg cag cgc tat gat tct aag ccc att gtg gac ctc att ggt gcc      320
Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp Leu Ile Gly Ala
                               10                15                20
atg gag acc cag tct gag ccc tct gag tta gaa ctg gac gat gtc gtt      368
Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu Asp Asp Val Val
                               25                30                35
atc acc aac ccc cac att gag gcc att ctg gag aat gaa gac tgg atc      416
Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn Glu Asp Trp Ile
40                45                50                55
gaa gat gcc tcg ggt ctc atg tcc cac tgc att gcc atc ttg aag att      464
Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala Ile Leu Lys Ile
                               60                65                70
tgt cac act ctg aca gag aag ctt gtt gcc atg aca atg ggc tct ggg      512
Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr Met Gly Ser Gly
                               75                80                85
gcc aag atg aag act tca gcc agt gtc agc gac atc att gtg gtg gcc      560
Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile Ile Val Val Ala
                               90                95                100
aag cgg atc agc ccc agg gtg gat gat gtt gtg aag tcg atg tac cct      608
Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys Ser Met Tyr Pro
                               105                110                115
ccg ttg gac ccc aaa ctc ctg gac gca cgg acg act gcc ctg ctc ctg      656
Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr Ala Leu Leu Leu
120                125                130                135
tct gtc agt cac ctg gtg ctg gtg aca agg aat gcc tgc cat ctg acg      704
Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala Cys His Leu Thr
                               140                145                150
gga ggc ctg gac tgg att gac cag tct ctg tcg gct gct gag gag cat      752
Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala Ala Glu Glu His
                               155                160                165

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80

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ttg gaa gtc ctt cga gaa gca gcc cta gct tct gag cca gat aaa ggc      800
Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu Pro Asp Lys Gly
      170              175              180
ctc cca ggc cct gaa ggc ttc ctg cag gag cag tct gca att      842
Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser Ala Ile
      185              190              195
tagtgcctac aggccagcag ctagccatga aggccccctgc cgccatccct ggatggctca    902
gcttagcctt ctactttttc ctatagagtt agttgttctc cacggctgga gagttcagct    962
gtgtgtgcat agtaaagcag gagatccccg tcagtttatg cctcttttgc agttgcaaac   1022
tgtggctggt gagtggcagt ctaatactac agttagggga gatgccattc actctctgca   1082
agaggagtat tgaaaactgg tggactgtca gctttattta gctcacctag tgttttcaag   1142
aaaattgagc caccgtctaa gaaatcaaga ggtttcacat taaaattaga atttctggcc   1202
tctctcgatc ggtcagaatg tgtggcaatt ctgatctgca ttttcagaag aggacaatca   1262
attgaaacta agtaggggtt tcttcttttg gcaagacttg tactctctca cctggcctgt   1322
ttcatttatt tgtattatct gcctgggtccc tgaggcgtct ggggtctctcc tctcccttgc  1382
aggtttgggt ttgaagctga ggaactacaa agttgatgat ttctttttta tctttatgcc   1442
tgcaatttta cctagctacc actagggtgga tagtaaattt atacttatgt ttcccccaaa   1502
aaaaaaaaaa aaa                                     1515
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<210> 48

<211> 1622

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 31..1248

<220>

<221> sig_peptide

<222> 31..135

<223> Von Heijne matrix

score 6.30

seq TLLLF AAPFGLLG/EK

<220>

<221> polyA_signal

<222> 1580..1585

<220>

<221> polyA_site

<222> 1607..1622

<400> 48

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aacctcttcc gtcggctgaa ttgcggccgt atg cgc ggc tct gtg gag tgc acc      54
                               Met Arg Gly Ser Val Glu Cys Thr
                               -35                -30

tgg ggt tgg ggg cac tgt gcc ccc agc ccc ctg ctc ctt tgg act cta      102
Trp Gly Trp Gly His Cys Ala Pro Ser Pro Leu Leu Leu Trp Thr Leu
      -25                -20                -15

ctt ctg ttt gca gcc cca ttt ggc ctg ctg ggg gag aag acc cgc cag      150
Leu Leu Phe Ala Ala Pro Phe Gly Leu Leu Gly Glu Lys Thr Arg Gln
      -10                -5                1                5

gtg tct ctg gag gtc atc cct aac tgg ctg ggc ccc ctg cag aac ctg      198
Val Ser Leu Glu Val Ile Pro Asn Trp Leu Gly Pro Leu Gln Asn Leu
              10              15              20

ctt cat ata cgg gca gtg ggc acc aat tcc aca ctg cac tat gtg tgg      246
Leu His Ile Arg Ala Val Gly Thr Asn Ser Thr Leu His Tyr Val Trp
              25              30              35

agc agc ctg ggg cct ctg gca gtg gta atg gtg gcc acc aac acc ccc      294
Ser Ser Leu Gly Pro Leu Ala Val Val Met Val Ala Thr Asn Thr Pro
              40              45              50

cac agc acc ctg agc gtc aac tgg agc ctc ctg cta tcc cct gag ccc      342
His Ser Thr Leu Ser Val Asn Trp Ser Leu Leu Leu Ser Pro Glu Pro
              55              60              65

gat ggg ggc ctg atg gtg ctc cct aag gac agc att cag ttt tct tct      390
Asp Gly Gly Leu Met Val Leu Pro Lys Asp Ser Ile Gln Phe Ser Ser
      70              75              80              85

gcc ctt gtt ttt acc agg ctg ctt gag ttt gac agc acc aac gtg tcc      438
Ala Leu Val Phe Thr Arg Leu Leu Glu Phe Asp Ser Thr Asn Val Ser
              90              95              100

gat acg gca gca aag cct ttg gga aga cca tat cct cca tac tcc ttg      486
Asp Thr Ala Ala Lys Pro Leu Gly Arg Pro Tyr Pro Pro Tyr Ser Leu
              105              110              115

gcc gat ttc tct tgg aac aac atc act gat tca ttg gat cct gcc acc      534
Ala Asp Phe Ser Trp Asn Asn Ile Thr Asp Ser Leu Asp Pro Ala Thr
              120              125              130

ctg agt gcc aca ttt caa ggc cac ccc atg aac gac cct acc agg act      582
Leu Ser Ala Thr Phe Gln Gly His Pro Met Asn Asp Pro Thr Arg Thr
              135              140              145

ttt gcc aat ggc agc ctg gcc ttc agg gtc cag gcc ttt tcc agg tcc      630
Phe Ala Asn Gly Ser Leu Ala Phe Arg Val Gln Ala Phe Ser Arg Ser
      150              155              160              165

agc cga cca gcc caa ccc cct cgc ctc ctg cac aca gca gac acc tgt      678

```

Ser Arg Pro Ala Gln Pro Pro Arg Leu Leu His Thr Ala Asp Thr Cys
 170 175 180
 cag cta gag gtg gcc ctg att gga gcc tct ccc cgg gga aac cgt tcc 726
 Gln Leu Glu Val Ala Leu Ile Gly Ala Ser Pro Arg Gly Asn Arg Ser
 185 190 195
 ctg ttt ggg ctg gag gta gcc aca ttg ggc cag ggc cct gac tgc ccc 774
 Leu Phe Gly Leu Glu Val Ala Thr Leu Gly Gln Gly Pro Asp Cys Pro
 200 205 210
 tca atg cag gag cag cac tcc atc gac gat gaa tat gca ccg gcc gtc 822
 Ser Met Gln Glu Gln His Ser Ile Asp Asp Glu Tyr Ala Pro Ala Val
 215 220 225
 ttc cag ttg gac cag cta ctg tgg ggc tcc ctc cca tca ggc ttt gca 870
 Phe Gln Leu Asp Gln Leu Leu Trp Gly Ser Leu Pro Ser Gly Phe Ala
 230 235 240 245
 cag tgg cga cca gtg gct tac tcc cag aag ccg ggg ggc cga gaa tca 918
 Gln Trp Arg Pro Val Ala Tyr Ser Gln Lys Pro Gly Gly Arg Glu Ser
 250 255 260
 gcc ctg ccc tgc caa gct tcc cct ctt cat cct gcc tta gca tac tct 966
 Ala Leu Pro Cys Gln Ala Ser Pro Leu His Pro Ala Leu Ala Tyr Ser
 265 270 275
 ctt ccc cag tca ccc att gtc cga gcc ttc ttt ggg tcc cag aat aac 1014
 Leu Pro Gln Ser Pro Ile Val Arg Ala Phe Phe Gly Ser Gln Asn Asn
 280 285 290
 ttc tgt gcc ttc aat ctg acg ttc ggg gct tcc aca ggc cct ggc tat 1062
 Phe Cys Ala Phe Asn Leu Thr Phe Gly Ala Ser Thr Gly Pro Gly Tyr
 295 300 305
 tgg gac caa cac tac ctc agc tgg tgg atg ctc ctg ggt gtg ggc ttc 1110
 Trp Asp Gln His Tyr Leu Ser Trp Ser Met Leu Leu Gly Val Gly Phe
 310 315 320 325
 cct cca gtg gac ggc ttg tcc cca cta gtc ctg ggc atc atg gca gtg 1158
 Pro Pro Val Asp Gly Leu Ser Pro Leu Val Leu Gly Ile Met Ala Val
 330 335 340
 gcc ctg ggt gcc cca ggg ctc atg ctg cta ggg ggc ggc ttg gtt ctg 1206
 Ala Leu Gly Ala Pro Gly Leu Met Leu Leu Gly Gly Gly Leu Val Leu
 345 350 355
 ctg ctg cac cac aag aag tac tca gag tac cag tcc ata aat 1248
 Leu Leu His His Lys Lys Tyr Ser Glu Tyr Gln Ser Ile Asn
 360 365 370
 taaggccgcg tctctggagg gaaggacatt actgaacctg tcttgctgtg cctcgaaact 1308
 ctggagggtg gagcatcaag ttccagcccc ctctactccc ccatcttgct tttctgtgga 1368
 acctcagagg ccagcctcga ctctctggag acccccaggt ggggcttcct tcatactttg 1428
 ttgggggact ttggaggcgg gcaggggaca gggtattga taaggteccc ttggtgttgc 1488

```

cttcttgcat ctccacacat ttcccttgga tgggacttgc aggcctaaat gagaggcatt 1548
ctgactgggt ggctgccctg gaaggcaaga aaatagattt attttttttt cacagggcaa 1608
aaaaaaaaaa aaaa 1622

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<210> 49

<211> 1448

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 131..490

<220>

<221> sig_peptide

<222> 131..301

<223> Von Heijne matrix

score 5.30

seq AIALATVLFLLGA/FL

<220>

<221> polyA_signal

<222> 1411..1416

<220>

<221> polyA_site

<222> 1434..1448

<400> 49

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ctgatccgc ctggggccgg ctgagtggca cttaagcggg ccatgccatg caaccttggg 60
cgctgccaac cgtgggcgag ctctgggtgt gggggcgccc tcgcgcggcg ctccgctgtg 120
tcagcgtgtt atg atg ccg tcc cgt acc aac ctg gct act gga atc ccc 169
      Met Met Pro Ser Arg Thr Asn Leu Ala Thr Gly Ile Pro
      -55              -50              -45
agt agt aaa gtg aaa tat tca agg ctc tcc agc aca gac gat ggc tac 217
Ser Ser Lys Val Lys Tyr Ser Arg Leu Ser Ser Thr Asp Asp Gly Tyr
      -40              -35              -30
att gac ctt cag ttt aag aaa acc cct cct aag atc cct tat aag gcc 265
Ile Asp Leu Gln Phe Lys Lys Thr Pro Pro Lys Ile Pro Tyr Lys Ala
      -25              -20              -15
atc gca ctt gcc act gtg ctg ttt ttg att ggc gcc ttt ctc att att 313
Ile Ala Leu Ala Thr Val Leu Phe Leu Ile Gly Ala Phe Leu Ile Ile

```

-10 5 1
ata ggc tcc ctc ctg ctg tca ggc tac atc agc aaa ggg ggg gca gac 361
Ile Gly Ser Leu Leu Leu Ser Gly Tyr Ile Ser Lys Gly Gly Ala Asp
5 10 15 20
cgg gcc gtt cca gtg ctg atc att ggc att ctg gtg ttc cta ccc gga 409
Arg Ala Val Pro Val Leu Ile Ile Gly Ile Leu Val Phe Leu Pro Gly
25 30 35
ttt tac cac ctg cgc atc gct tac tat gca tcc aaa ggc tac cgt ggt 457
Phe Tyr His Leu Arg Ile Ala Tyr Tyr Ala Ser Lys Gly Tyr Arg Gly
40 45 50
tac tcc tat gat gac att cca gac ttt gat gac tagcaccac cccatagctg 510
Tyr Ser Tyr Asp Asp Ile Pro Asp Phe Asp Asp
55 60
aggaggagtc acagtggaac tgtcccagct ttaagatatc tagcagaaac tatagctgag 570
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cttcccaaag atgttaagtg aacctacagt tagctaatta ggacaagctc tatttttcat 690
ccctggggccc tgacaagtgt ttccacagga atatgtatca tggaagaata gaggttattc 750
tgtaatggaa aagtgttgcc tgccaccacc ctctgtagag ctgagcattt cttttaaata 810
gtcttcattg ccaatttggt cttgtagcaa atggaacaat gtggtatggc taatttctta 870
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agattattcc tttaacggcc ggacttttgg ctgtttccta atgaaacatg tagtggttat 1230
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ttccaaggat cagcctggat gcctagagga ctagatcacc ttagtttgat tctatttttt 1350
agcttgcaaa aagtgactta tattccaaag aaattaaaat gttgaaatcc aaatcctaga 1410
aataaaatga gttaacttca aacaaaaaaaa aaaaaaaaa 1448

<210> 50

<211> 894

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 61..690

<220>

<221> sig_peptide

<222> 61..168

<223> Von Heijne matrix

score 4.60

seq GTVVLVAGTLCFA/WW

<220>

<221> polyA_signal

<222> 858..863

<220>

<221> polyA_site

<222> 879..894

<400> 50

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atg gcc ctg ccc cag atg tgt gac ggg agc cac ttg gcc tcc acc ctc      108
Met Ala Leu Pro Gln Met Cys Asp Gly Ser His Leu Ala Ser Thr Leu
      -35              -30              -25
cgc tat tgc atg aca gtc agc ggc aca gtg gtt ctg gtg gcc ggg acg      156
Arg Tyr Cys Met Thr Val Ser Gly Thr Val Val Leu Val Ala Gly Thr
      -20              -15              -10              -5
ctc tgc ttc gct tgg tgg agc gaa ggg gat gca acc gcc cag cct ggc      204
Leu Cys Phe Ala Trp Trp Ser Glu Gly Asp Ala Thr Ala Gln Pro Gly
              1              5              10
cag ctg gcc cca ccc acg gag tat ccg gtg cct gag ggc ccc agc ccc      252
Gln Leu Ala Pro Pro Thr Glu Tyr Pro Val Pro Glu Gly Pro Ser Pro
              15              20              25
ctg ctc agg tcc gtc agc ttc gtc tgc tgc ggt gca ggt ggc ctg ctg      300
Leu Leu Arg Ser Val Ser Phe Val Cys Cys Gly Ala Gly Gly Leu Leu
              30              35              40
ctg ctc att ggc ctg ctg tgg tcc gtc aag gcc agc atc cca ggg cca      348
Leu Leu Ile Gly Leu Leu Trp Ser Val Lys Ala Ser Ile Pro Gly Pro
      45              50              55              60
cct cga tgg gac ccc tat cac ctc tcc aga gac ctg tac tac ctc act      396
Pro Arg Trp Asp Pro Tyr His Leu Ser Arg Asp Leu Tyr Tyr Leu Thr
              65              70              75
gtg gag tcc tca gag aag gag agc tgc agg acc ccc aaa gtg gtt gac      444
Val Glu Ser Ser Glu Lys Glu Ser Cys Arg Thr Pro Lys Val Val Asp
              80              85              90
atc ccc act tac gag gaa gcc gtg agc ttc cca gtg gcc gag ggg ccc      492
Ile Pro Thr Tyr Glu Glu Ala Val Ser Phe Pro Val Ala Glu Gly Pro
              95              100              105
cca aca cca cct gca tac cct acg gag gaa gcc ctg gag cca agt gga      540

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Pro Thr Pro Pro Ala Tyr Pro Thr Glu Glu Ala Leu Glu Pro Ser Gly
      110                115                120
tcg agg gat gcc ctg ctc agc acc cag ccc gcc tgg cct cca ccc agc      588
Ser Arg Asp Ala Leu Leu Ser Thr Gln Pro Ala Trp Pro Pro Pro Ser
125                130                135                140
tat gag agc atc agc ctt gct ctt gat gcc gtt tct gca gag acg aca      636
Tyr Glu Ser Ile Ser Leu Ala Leu Asp Ala Val Ser Ala Glu Thr Thr
      145                150                155
ccg agt gcc aca cgc tcc tgc tca ggc ctg gtt cag act gca cgg gga      684
Pro Ser Ala Thr Arg Ser Cys Ser Gly Leu Val Gln Thr Ala Arg Gly
      160                165                170
gga agt taaaggctcc tagcaggctcc tgaatccaga gacaaaaatg ctgtgccttc      740
Gly Ser
tccagagtct tatgcagtgc ctgggacaca gtaggcactc agcaaacggt cgttgttgaa      800
ggctgttcta tttatctatt gctgtataac aaaccacccc agaatttagt ggcttaaaat      860
aaatccatt ttattacgaa aaaaaaaaaa aaaa      894

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<210> 51

<211> 1447

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 501..1253

<220>

<221> sig_peptide

<222> 501..1229

<223> Von Heijne matrix

score 4.10

seq LPSLAHLPALDC/LE

<220>

<221> polyA_signal

<222> 1392..1397

<220>

<221> polyA_site

<222> 1432..1447

<220>

<221> misc_feature

<222> 243,252,278,285,387,1429

<223> n=a, g, c or t

<400> 51

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agaagggggac ccaaggggtc ggccgcggcc aaggccccta ggaccgccgc cccagctcac      120
gctgccgacg gcagctatag acattctgcg tcaggtccgg gctcctggac ttgaccttc      180
ccgagccctg gaggtgggga gaaaagggtc accaattttt aaaatccaaa tatactcat      240
ggntacagtg gnaagaactg gccagagagt ctggaagntt tgggnttctg gtcctggctg      300
tgccactgac tcactgtgac cttgggatct tgtgctgtga agacatttcc caagtgttc      360
atgttagcca gcaaactctga cccacanggc ctggaaagag gtgattgtta ggttgccgac      420
aggtggtctt atccagctca gcttcccctg ggacccaccg tgggacctga ggcagaactg      480
gggtggactt ggctcctcc atg gca cac cgg ctg cag ata cga ctg ctg acg      533
          Met Ala His Arg Leu Gln Ile Arg Leu Leu Thr
                    -240                    -235

tgg gat gtg aag gac acg ctg ctc agg ctc cgc cac ccc tta ggg gag      581
Trp Asp Val Lys Asp Thr Leu Leu Arg Leu Arg His Pro Leu Gly Glu
          -230          -225          -220

gcc tat gcc acc aag gcc cgg gcc cat ggg ctg gag gtg gag ccc tca      629
Ala Tyr Ala Thr Lys Ala Arg Ala His Gly Leu Glu Val Glu Pro Ser
          -215          -210          -205

gcc ctg gaa caa ggc ttc agg cag gca tac agg gct cag agc cac agc      677
Ala Leu Glu Gln Gly Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser
          -200          -195          -190          -185

ttc ccc aac tac ggc ctg agc cac ggc cta acc tcc cgc cag tgg tgg      725
Phe Pro Asn Tyr Gly Leu Ser His Gly Leu Thr Ser Arg Gln Trp Trp
          -180          -175          -170

ctg gat gtg gtc ctg cag acc ttc cac ctg gcg ggt gtc cag gat gct      773
Leu Asp Val Val Leu Gln Thr Phe His Leu Ala Gly Val Gln Asp Ala
          -165          -160          -155

cag gct gta gcc ccc atc gct gaa cag ctt tat aaa gac ttc agc cac      821
Gln Ala Val Ala Pro Ile Ala Glu Gln Leu Tyr Lys Asp Phe Ser His
          -150          -145          -140

ccc tgc acc tgg cag gtg ttg gat ggg gct gag gac acc ctg agg gag      869
Pro Cys Thr Trp Gln Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu
          -135          -130          -125

tgc cgc aca cgg ggt ctg aga ctg gca gtg atc tcc aac ttt gac cga      917
Cys Arg Thr Arg Gly Leu Arg Leu Ala Val Ile Ser Asn Phe Asp Arg
          -120          -115          -110          -105

cgg cta gag ggc atc ctg gag ggc ctt ggc ctg cgt gaa cac ttc gac      965
Arg Leu Glu Gly Ile Leu Glu Gly Leu Gly Leu Arg Glu His Phe Asp

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88

-100 -95 -90

ttt gtg ctg acc tcc gag gct gct ggc tgg ccc aag ccg gac ccc cgc 1013
Phe Val Leu Thr Ser Glu Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg

-85 -80 -75

att ttc cag gag gcc ttg cgg ctt gct cat atg gaa cca gta gtg gca 1061
Ile Phe Gln Glu Ala Leu Arg Leu Ala His Met Glu Pro Val Val Ala

-70 -65 -60

gcc cat gtt ggg gat aat tac ctc tgc gat tac cag ggg cct cgg gct 1109
Ala His Val Gly Asp Asn Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala

-55 -50 -45

gtg ggc atg cac agc ttc ctg gtg gtt ggc cca cag gca ctg gac ccc 1157
Val Gly Met His Ser Phe Leu Val Val Gly Pro Gln Ala Leu Asp Pro

-40 -35 -30 -25

gtg gtc agg gat tct gta cct aaa gaa cac atc ctc ccc tct ctg gcc 1205
Val Val Arg Asp Ser Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala

-20 -15 -10

cat ctc ctg cct gcc ctt gac tgc cta gag ggc tca act cca ggg ctt 1253
His Leu Leu Pro Ala Leu Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu

-5 1 5

tgaggccagt gagggaagtg gctgggcctt aggccatgga gaaaacctta aacaaaccct 1313
ggagacaggg agccccttct ttctccacag ctctggacct ttccccctct cctgcgggcc 1373
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aaaaaaaaaaaa 1447

<210> 52

<211> 1540

<212> DNA

<213> Homo Sapiens

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<221> CDS

<222> 25..402

<220>

<221> sig_peptide

<222> 25..96

<223> Von Heijne matrix

score 7.00

seq LLCCFRALSGSLs/MR

<220>

<221> polyA_signal

<222> 1500..1505

<220>

<221> polyA_site

<222> 1525..1540

<220>

<221> misc_feature

<222> 625,1411,1432,1440,1450,1506

<223> n=a, g, c or t

<400> 52

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 Met Asp Lys Ser Leu Leu Leu Glu Leu

-20

ccc atc ctg ctc tgc tgc ttt agg gca tta tct gga tca ctt tca atg 99
 Pro Ile Leu Leu Cys Cys Phe Arg Ala Leu Ser Gly Ser Leu Ser Met

-15 -10 -5 1
 aga aat gat gca gtc aat gaa ata gtt gct gtg aaa aac aat ttt cct 147
 Arg Asn Asp Ala Val Asn Glu Ile Val Ala Val Lys Asn Asn Phe Pro

5

10

15

gtg ata gaa att att cag tgt agg atg tgc cac ctc cag ttc cca gga 195
 Val Ile Glu Ile Ile Gln Cys Arg Met Cys His Leu Gln Phe Pro Gly

20

25

30

gaa aag tgc tcc aga gga aga gga ata tgc aca gca aca aca gaa gag 243
 Glu Lys Cys Ser Arg Gly Arg Gly Ile Cys Thr Ala Thr Thr Glu Glu

35

40

45

gcc tgc atg gtt gga agg atg ttc aaa agg gat ggt aat ccc tgg tta 291
 Ala Cys Met Val Gly Arg Met Phe Lys Arg Asp Gly Asn Pro Trp Leu

50

55

60

65

acc ttc atg ggc tgc cta aag aac tgt gct gat gtg aaa ggc ata agg 339
 Thr Phe Met Gly Cys Leu Lys Asn Cys Ala Asp Val Lys Gly Ile Arg

70

75

80

tgg agt gtc tat ttg gtg aac ttc agg tgc tgc agg agc cat gac ctg 387
 Trp Ser Val Tyr Leu Val Asn Phe Arg Cys Cys Arg Ser His Asp Leu

85

90

95

tgc aat gaa gac ctt tagaagttaa tgggtcttct gtgactccaa tttctgggtg 442
 Cys Asn Glu Asp Leu

100

aggtgtgtgc ctcagcctct tcacaatgac tttctaaaaa aaatcacaca cacacacaca 502

cacactacag aagaggattg caaacacatg gctccatctt ctgcacacga aaggaaagtc 562

cctctccttt tctacagtct ctgtcacgcc ccttaaaata agtaataaaa taaccttgag 622

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agnaaagaac aagatcaata tatcctgcag gttgctacaa acccttgtgc ttctactgta 682
tagccagttc attcagaaaa ggaggaaagg gtagtttaat ttcaaaaaag aatcccttcc 742
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ctaaaaaaaa aaaaaaaaa 1540
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<210> 53

<211> 1643

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 280..678

<220>

<221> sig_peptide

<222> 280..411

<223> Von Heijne matrix

score 3.90

seq LSDSLWSPHCSWS/ER

<220>

<221> polyA_signal

<222> 1606..1611

<220>

<221> polyA_site

<222> 1628..1643

<400> 53

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 atccattttt catgccatta ctttatttaa aaacctgggc caaccagtt ctcaaaaggt 180
 attggacatc ctcagaaaag atgactgtc tatgttgaac caaacaactg attcttacag 240
 gtttcttct cacttgctct ctggctgtgg cagccagat atg gac agg aga gct 294
 Met Asp Arg Arg Ala
 -40
 aca tcc ttc cct cca ctc cct gcc aaa gaa agg aga gct ggg ata agc 342
 Thr Ser Phe Pro Pro Leu Pro Ala Lys Glu Arg Arg Ala Gly Ile Ser
 -35 -30 -25
 agt gcc ctc ccc tgc cca ccc act atg tca ctt tct gac tcc ctt tgg 390
 Ser Ala Leu Pro Cys Pro Pro Thr Met Ser Leu Ser Asp Ser Leu Trp
 -20 -15 -10
 tcc cct cat tgc tct tgg agt gag aga cct cat tcc ttc tct cac tgg 438
 Ser Pro His Cys Ser Trp Ser Glu Arg Pro His Ser Phe Ser His Trp
 -5 1 5
 agg cag cca aga atg gga tcc tct ggt ggg tct ttg gat tat gta agt 486
 Arg Gln Pro Arg Met Gly Ser Ser Gly Gly Ser Leu Asp Tyr Val Ser
 10 15 20 25
 ttc aaa cac tgg ata cac agc tcc aga tct aaa ggc aag att gct gct 534
 Phe Lys His Trp Ile His Ser Ser Arg Ser Lys Gly Lys Ile Ala Ala
 30 35 40
 cta gag gca gga ctg ttc att tcc tgc ctt ggg gat gca ccc aga ggc 582
 Leu Glu Ala Gly Leu Phe Ile Ser Cys Leu Gly Asp Ala Pro Arg Gly
 45 50 55
 ctg aat gct tcc caa gga aac caa aga aag aac atg gtc tgt ttc aga 630
 Leu Asn Ala Ser Gln Gly Asn Gln Arg Lys Asn Met Val Cys Phe Arg
 60 65 70
 ggt gga gtg gcc agt cta gct ctg cca tct ctc act cct tcc tgc ctt 678
 Gly Gly Val Ala Ser Leu Ala Leu Pro Ser Leu Thr Pro Ser Cys Leu
 75 80 85
 tagggtagga ctgaggtgga aagcctgaac tgctgtctct gctctggctt gtgctcaagc 738
 tgtgtgtcct tggactggcc atctctctctc tgcaaccctc ggtcttctca ttgtataaat 798
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 ggttcaagcg attctcctgc ctcagcctcc cgagtagctg ggattacagg cgcgtgactc 1338

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catgcctggc taatTTTTgt atttttagta gaggtagggt ttcacatgt tgaccagggt 1398
ggtctggaac tcctgatctc aggtgatctg cctgcctcca cctcccaaag tgctggaatt 1458
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tcaaatacccc aactttcttc caagaggaat ttcaagaaac actgaccaat ctggttacag 1578
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aaaaa 1643

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<210> 54

<211> 1314

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 64..726

<220>

<221> sig_peptide

<222> 64..147

<223> Von Heijne matrix

score 3.70

seq VVFTLGMFSAAGLS/DL

<220>

<221> polyA_signal

<222> 1279..1284

<220>

<221> polyA_site

<222> 1300..1314

<400> 54

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gta atg gag gcg ggc ggc ttt ctg gac tcg ctc att tac gga gca tgc 108
      Met Glu Ala Gly Gly Phe Leu Asp Ser Leu Ile Tyr Gly Ala Cys
              -25              -20              -15
gtg gtc ttc acc ctt ggc atg ttc tcc gcc ggc ctc tcg gac ctc agg 156
Val Val Phe Thr Leu Gly Met Phe Ser Ala Gly Leu Ser Asp Leu Arg
              -10              -5              1
cac atg cga atg acc cgg agt gtg gac aac gtc cag ttc ctg ccc ttt 204
His Met Arg Met Thr Arg Ser Val Asp Asn Val Gln Phe Leu Pro Phe
      5              10              15

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ctc acc acg gaa gtc aac aac ctg ggc tgg ctg agt tat ggg gct ttg 252
 Leu Thr Thr Glu Val Asn Asn Leu Gly Trp Leu Ser Tyr Gly Ala Leu
 20 25 30 35
 aag gga gac ggg atc ctc atc gtc gtc aac aca gtg ggt gct gcg ctt 300
 Lys Gly Asp Gly Ile Leu Ile Val Val Asn Thr Val Gly Ala Ala Leu
 40 45 50
 cag acc ctg tat atc ttg gca tat ctg cat tac tgc cct cgg aag cgt 348
 Gln Thr Leu Tyr Ile Leu Ala Tyr Leu His Tyr Cys Pro Arg Lys Arg
 55 60 65
 gtt gtg ctc cta cag act gca acc ctg cta ggg gtc ctt ctc ctg ggt 396
 Val Val Leu Leu Gln Thr Ala Thr Leu Leu Gly Val Leu Leu Leu Gly
 70 75 80
 tat ggc tac ttt tgg ctc ctg gta ccc aac cct gag gcc cgg ctt cag 444
 Tyr Gly Tyr Phe Trp Leu Leu Val Pro Asn Pro Glu Ala Arg Leu Gln
 85 90 95
 cag ttg ggc ctc ttc tgc agt gtc ttc acc atc agc atg tac ctc tca 492
 Gln Leu Gly Leu Phe Cys Ser Val Phe Thr Ile Ser Met Tyr Leu Ser
 100 105 110 115
 cca ctg gct gac ttg gct aag gtg att caa act aaa tca acc caa tgt 540
 Pro Leu Ala Asp Leu Ala Lys Val Ile Gln Thr Lys Ser Thr Gln Cys
 120 125 130
 ctc tcc tac cca ctc acc att gct acc ctt ctc acc tct gcc tcc tgg 588
 Leu Ser Tyr Pro Leu Thr Ile Ala Thr Leu Leu Thr Ser Ala Ser Trp
 135 140 145
 tgc ctc tat ggg ttt cga ctc aga gat ccc tat atc atg gtg tcc aac 636
 Cys Leu Tyr Gly Phe Arg Leu Arg Asp Pro Tyr Ile Met Val Ser Asn
 150 155 160
 ttt cca gga atc gtc acc agc ttt atc cgc ttc tgg ctt ttc tgg aag 684
 Phe Pro Gly Ile Val Thr Ser Phe Ile Arg Phe Trp Leu Phe Trp Lys
 165 170 175
 tac ccc cag gag caa gac agg aac tac tgg ctc ctg caa acc 726
 Tyr Pro Gln Glu Gln Asp Arg Asn Tyr Trp Leu Leu Gln Thr
 180 185 190
 tgaggtgct catctgacca ctgggcacct tagtgccaac ctgaaccaa gagacctcct 786
 tgtttcagct gggcctgctg tccagcttcc caggtgcagt gggttgtggg aacaagagat 846
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 gagatgaaat cacttttttat tttttagaga tttttttttt ttaatttttg aggttggggt 966
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 aacatggtga aaccccatct ctactaaaaa tacaaaaatta gccaggcatg atggcacatg 1146
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aatatgcctt aaaataaagt gttccccacc cctaaaaaaaa aaaaaaaaa

1314

<210> 55

<211> 2356

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 42..1097

<220>

<221> sig_peptide

<222> 42..110

<223> Von Heijne matrix

score 4.40

seq QFILLGTTSVVTAL

<220>

<221> polyA_signal

<222> 2323..2328

<220>

<221> polyA_site

<222> 2341..2356

<400> 55

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Met Glu Ser Gly Gly

-20

egg ccc tcg ctg tgc cag ttc atc ctc ctg ggc acc acc tct gtg gtc 104

Arg Pro Ser Leu Cys Gln Phe Ile Leu Leu Gly Thr Thr Ser Val Val

-15

-10

-5

acc gcc gcc ctg tac tcc gtg tac cgg cag aag gcc cgg gtc tcc caa 152

Thr Ala Ala Leu Tyr Ser Val Tyr Arg Gln Lys Ala Arg Val Ser Gln

1

5

10

gag ctc aag gga gct aaa aaa gtt cat ttg ggt gaa gat tta aag agt 200

Glu Leu Lys Gly Ala Lys Lys Val His Leu Gly Glu Asp Leu Lys Ser

15

20

25

30

att ctt tca gaa gct cca gga aaa tgc gtg cct tat gct gtt ata gaa 248

Ile Leu Ser Glu Ala Pro Gly Lys Cys Val Pro Tyr Ala Val Ile Glu

35

40

45

gga gct gtg cgg tct gtt aaa gaa acg ctt aac agc cag ttt gtg gaa	296
Gly Ala Val Arg Ser Val Lys Glu Thr Leu Asn Ser Gln Phe Val Glu	
50 55 60	
aac tgc aag ggg gta att cag cgg ctg aca ctt cag gag cac aag atg	344
Asn Cys Lys Gly Val Ile Gln Arg Leu Thr Leu Gln Glu His Lys Met	
65 70 75	
gtg tgg aat cga acc acc cac ctt tgg aat gat tgc tca aag atc att	392
Val Trp Asn Arg Thr Thr His Leu Trp Asn Asp Cys Ser Lys Ile Ile	
80 85 90	
cat cag agg acc aac aca gtg ccc ttt gac ctg gtg ccc cac gag gat	440
His Gln Arg Thr Asn Thr Val Pro Phe Asp Leu Val Pro His Glu Asp	
95 100 105 110	
ggc gtg gat gtg gct gtg cga gtg ctg aag ccc ctg gac tca gtg gat	488
Gly Val Asp Val Ala Val Arg Val Leu Lys Pro Leu Asp Ser Val Asp	
115 120 125	
ctg ggt cta gag act gtg tat gag aag ttc cac ccc tcg att cag tcc	536
Leu Gly Leu Glu Thr Val Tyr Glu Lys Phe His Pro Ser Ile Gln Ser	
130 135 140	
ttc acc gat gtc atc ggc cac tac atc agc ggt gag cgg ccc aaa ggc	584
Phe Thr Asp Val Ile Gly His Tyr Ile Ser Gly Glu Arg Pro Lys Gly	
145 150 155	
atc caa gag acc gag gag atg ctg aag gtg ggg gcc acc ctc aca ggg	632
Ile Gln Glu Thr Glu Glu Met Leu Lys Val Gly Ala Thr Leu Thr Gly	
160 165 170	
gtt ggc gaa ctg gtc ctg gac aac aac tct gtc cgc ctg cag ccg ccc	680
Val Gly Glu Leu Val Leu Asp Asn Asn Ser Val Arg Leu Gln Pro Pro	
175 180 185 190	
aaa caa ggc atg cag tac tat cta agc agc cag gac ttc gac agc ctg	728
Lys Gln Gly Met Gln Tyr Tyr Leu Ser Ser Gln Asp Phe Asp Ser Leu	
195 200 205	
ctg cag agg cag gag tcg agc gtc agg ctc tgg aag gtg ctg gcg ctg	776
Leu Gln Arg Gln Glu Ser Ser Val Arg Leu Trp Lys Val Leu Ala Leu	
210 215 220	
gtt ttt ggc ttt gcc aca tgt gcc acc ctc ttc ttc att ctc cgg aag	824
Val Phe Gly Phe Ala Thr Cys Ala Thr Leu Phe Phe Ile Leu Arg Lys	
225 230 235	
cag tat ctg cag cgg cag gag cgc ctg cgc ctc aag cag atg cag gag	872
Gln Tyr Leu Gln Arg Gln Glu Arg Leu Arg Leu Lys Gln Met Gln Glu	
240 245 250	
gag ttc cag gag cat gag gcc cag ctg ctg agc cga gcc aag cct gag	920
Glu Phe Gln Glu His Glu Ala Gln Leu Leu Ser Arg Ala Lys Pro Glu	
255 260 265 270	

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gac agg gag agt ctg aag agc gcc tgt gta gtg tgt ctg agc agc ttc      968
Asp Arg Glu Ser Leu Lys Ser Ala Cys Val Val Cys Leu Ser Ser Phe
                275                280                285
aag tcc tgc gtc ttt ctg gag tgt ggg cac gtt tgt tcc tgc acc gag      1016
Lys Ser Cys Val Phe Leu Glu Cys Gly His Val Cys Ser Cys Thr Glu
                290                295                300
tgc tac cgc gcc ttg cca gag ccc aag aag tgc cct atc tgc aga cag      1064
Cys Tyr Arg Ala Leu Pro Glu Pro Lys Lys Cys Pro Ile Cys Arg Gln
                305                310                315
gcg atc acc cgg gtg ata ccc ctg tac aac agc taatagtttg gaagccgcac      1117
Ala Ile Thr Arg Val Ile Pro Leu Tyr Asn Ser
                320                325
agcttgacct ggaagcacc ctgccccctt ttcagggatt tttatctcga ggcctttgga      1177
ggagcagtggt tgggggtagc tgtcaacctc aggtatgatt gagggaggaa ttgggtagaa      1237
actctccaga cccatgcctc caatggcagg atgtgcctt tcccacctga gaggggaccc      1297
tgtccatgtg cagcctcatc agagcctcac cctgggagga tgccgtggcg tctcctccca      1357
ggagccagat cagtgcgagt gtgactgaaa atgcctcatc acttaagcac caaagccagt      1417
gatcagcagc tcttctgttc ctgtgtcttc tgtttttttc tggggaatcg ttgcttgctg      1477
tggacttggt ggaggactca gaggggagga aaggctgggc cccgagtaca acggatgcct      1537
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cacttgggag agctcggggt ggtccctggt tttccctcct ggagaatgag gcgcagaggc      1897
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ccttgcaagg ctgtcacaag gaaaagcagc cggctggcac cctgagcata tgccctcttg      2017
gggctccttc atccagcccg tcgcagcttt gacatcttgg tgtactcatg tcgcttctcc      2077
ttgtgttacc cctcccagat attaccattt gccctcacc tgcccttggt gagcctttta      2137
gtgcaagaca gatggggctg ttttccccca cctctgagta gttggaggtc acatacacag      2197
ctcttttttt attgccttt tctgcctctg aatgttcac tctcgtcttc ctttgtgcag      2257
gcgaggaagg ggtgccttca ggggccgaca ctagtatgat gcagtgtcca gtgtgaacag      2317
cagaaattaa acatgttgca accaaaaaaa aaaaaaaaaa      2356

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<210> 56

<211> 1701

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 245..1399

<220>
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 <222> 245..796
 <223> Von Heijne matrix
 score 5.10
 seq GWLPLLLLSLLVA/TW

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 <221> polyA_signal
 <222> 1669..1674

<220>
 <221> polyA_site
 <222> 1687..1701

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 agcgccgtac cccgagagcc gaccgttcaa tgtggctctg aaactgggcc atctccagag 120
 tggatgctac aacatgatct aatcccgga gacttgaggg acctccgagt agaacctgtt 180
 acaactagtg ttgcaacagg ggactattca attttgatga atgtaagctg ggtactccgg 240
 gcag atg tgg aca ttt tcc tac atc ggc ttc cct gta gag ctg aac aca 289
 Met Trp Thr Phe Ser Tyr Ile Gly Phe Pro Val Glu Leu Asn Thr
 -180 -175 -170
 gtc tat ttc att ggg gcc cat aaa att cct aat gca aat atg aat gaa 337
 Val Tyr Phe Ile Gly Ala His Lys Ile Pro Asn Ala Asn Met Asn Glu
 -165 -160 -155
 gat ggc cct tcc atg tct gtg aat ttc acc tca cca ggc tgc cta gac 385
 Asp Gly Pro Ser Met Ser Val Asn Phe Thr Ser Pro Gly Cys Leu Asp
 -150 -145 -140
 cac ata atg aaa tat aaa aaa aag tgt gtc aag gcc gga agc ctg tgg 433
 His Ile Met Lys Tyr Lys Lys Lys Cys Val Lys Ala Gly Ser Leu Trp
 -135 -130 -125
 gat ccg aac atc act gct tgt aag aag aat gag gag aca gta gaa gtg 481
 Asp Pro Asn Ile Thr Ala Cys Lys Lys Asn Glu Glu Thr Val Glu Val
 -120 -115 -110
 aac ttc aca acc act ccc ctg gga aac aga tac atg gct ctt atc caa 529
 Asn Phe Thr Thr Thr Pro Leu Gly Asn Arg Tyr Met Ala Leu Ile Gln
 -105 -100 -95 -90
 cac agc act atc atc ggg ttt tct cag gtg ttt gag cca cac cag aag 577
 His Ser Thr Ile Ile Gly Phe Ser Gln Val Phe Glu Pro His Gln Lys
 -85 -80 -75

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aaa caa acg cga gct tca gtg gtg att cca gtg act ggg gat agt gaa      625
Lys Gln Thr Arg Ala Ser Val Val Ile Pro Val Thr Gly Asp Ser Glu
      -70      -65      -60

ggg gct acg gtg cag ctg act cca tat ttt cct act tgt ggc agc gac      673
Gly Ala Thr Val Gln Leu Thr Pro Tyr Phe Pro Thr Cys Gly Ser Asp
      -55      -50      -45

tgc atc cga cat aaa gga aca gtt gtg ctc tgc cca caa aca ggc gtc      721
Cys Ile Arg His Lys Gly Thr Val Val Leu Cys Pro Gln Thr Gly Val
      -40      -35      -30

cct ttc cct ctg gat aac aac aaa agc aag cgg gga ggc tgg ctg cct      769
Pro Phe Pro Leu Asp Asn Asn Lys Ser Lys Pro Gly Gly Trp Leu Pro
      -25      -20      -15      -10

ctc ctc ctg ctg tct ctg ctg gtg gcc aca tgg gtg ctg gtg gca ggg      817
Leu Leu Leu Leu Ser Leu Leu Val Ala Thr Trp Val Leu Val Ala Gly
      -5      1      5

atc tat cta atg tgg agg cac gaa agg atc aag aag act tcc ttt tct      865
Ile Tyr Leu Met Trp Arg His Glu Arg Ile Lys Lys Thr Ser Phe Ser
      10      15      20

acc acc aca cta ctg ccc ccc att aag gtt ctt gtg gtt tac cca tct      913
Thr Thr Thr Leu Leu Pro Pro Ile Lys Val Leu Val Val Tyr Pro Ser
      25      30      35

gaa ata tgt ttc cat cac aca att tgt tac ttc act gaa ttt ctt caa      961
Glu Ile Cys Phe His His Thr Ile Cys Tyr Phe Thr Glu Phe Leu Gln
      40      45      50      55

aac cat tgc aga agt gag gtc atc ctt gaa aag tgg cag aaa aag aaa      1009
Asn His Cys Arg Ser Glu Val Ile Leu Glu Lys Trp Gln Lys Lys Lys
      60      65      70

ata gca gag atg ggt cca gtg cag tgg ctt gcc act caa aag aag gca      1057
Ile Ala Glu Met Gly Pro Val Gln Trp Leu Ala Thr Gln Lys Lys Ala
      75      80      85

gca gac aaa gtc gtc ttc ctt ctt tcc aat gac gtc aac agt gtg tgc      1105
Ala Asp Lys Val Val Phe Leu Leu Ser Asn Asp Val Asn Ser Val Cys
      90      95      100

gat ggt acc tgt ggc aag agc gag ggc agt ccc agt gag aac tct caa      1153
Asp Gly Thr Cys Gly Lys Ser Glu Gly Ser Pro Ser Glu Asn Ser Gln
      105      110      115

gac ctc ttc ccc ctt gcc ttt aac ctt ttc tgc agt gat cta aga agc      1201
Asp Leu Phe Pro Leu Ala Phe Asn Leu Phe Cys Ser Asp Leu Arg Ser
      120      125      130      135

cag att cat ctg cac aaa tac gtg gtg gtc tac ttt aga gag att gat      1249
Gln Ile His Leu His Lys Tyr Val Val Val Tyr Phe Arg Glu Ile Asp
      140      145      150

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aca aaa gac gat tac aat gct ctc agt gtc tgc ccc aag tac cac ctc 1297
Thr Lys Asp Asp Tyr Asn Ala Leu Ser Val Cys Pro Lys Tyr His Leu
155 160 165
atg aag gat gcc act gct ttc tgt gca gaa ctt ctc cat gtc aag cag 1345
Met Lys Asp Ala Thr Ala Phe Cys Ala Glu Leu Leu His Val Lys Gln
170 175 180
cag gtg tca gca gga aaa aga tca caa gcc tgc cac gat ggc tgc tgc 1393
Gln Val Ser Ala Gly Lys Arg Ser Gln Ala Cys His Asp Gly Cys Cys
185 190 195
tcc ttg tagccacccc atgagaagca agagacctta aaggcttcct atcccaccaa 1449
Ser Leu
200
ttacagggaa aaaacgtgtg atgacctga agcttactat gcagcctaca aacagcctta 1509
gtaattaaaa cattttatac caataaaaatt ttcaaataatt gctaaactaat gtagcattaa 1569
ctaacgattg gaaactacat ttacaacttc aaagctgttt tatacataga aatcaattac 1629
agttttaatt gaaaactata accattttga taatgcaaca ataaagcatc ttcagccaaa 1689
aaaaaaaaaa aa 1701

<210> 57

<211> 772

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 235..441

<220>

<221> sig_peptide

<222> 235..303

<223> Von Heijne matrix

score 5.30

seq LLLDVTVPFIPALP/FS

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<221> polyA_site

<222> 758..772

<220>

<221> misc_feature

<222> 573

<223> n=a, g, c or t

<400> 57

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 ccctaaccctc tgggaagaaa atatccacaa tgaaatttct acaagattag aggaaggaga 120
 gaggcaacgg ggattccatt tctactagga gtatcaacct ctgagaggga tatatccatc 180
 tctgtggatg tcattctgctc tgcagaaaac cctttcttgg aactaccagg aaac atg 237

Met

aat ctg atg tgg acc ctg ctg ctt ttc ctg ctt ttg gac gta act gtc 285
 Asn Leu Met Trp Thr Leu Leu Leu Phe Leu Leu Leu Asp Val Thr Val

-20

-15

-10

ttc att cca gcc ctg ccc ttc tca aca cga cat ata gac aac ccc agg 333
 Phe Ile Pro Ala Leu Pro Phe Ser Thr Arg His Ile Asp Asn Pro Arg

-5

1

5

10

tgg tgg gtc cct aga gga cac cac cga tac tgt gat gtg atg atg agg 381
 Ser Trp Val Pro Arg Gly His His Arg Tyr Cys Asp Val Met Met Arg

15

20

25

cgc cgt tgg ctg atc tat agg ggt aaa tgc gag cag atc cac aca ttc 429
 Arg Arg Trp Leu Ile Tyr Arg Gly Lys Cys Glu Gln Ile His Thr Phe

30

35

40

att cat aga atc tgaccaccat agcagatttc tgcagaactc caccactgcc 481

Ile His Arg Ile

45

ctgtaccaac agccctccca tgtgcagctg ccacaacagt actcatgatg tcaatgtcac 541
 tgactgcttt gccagcacag ggaccgcgacc tnttactgc cactaccaa aataaggagt 601
 ccaccaggcc catgcgagtg ggctgcaaga agggggcctc tgttcacctg gatggctagg 661
 ttctctctga caacggcacc tgaatgactt gcaccctacg ccttcaaate tgtgcagcac 721
 tgtcaaggtc ttctttgtaa atgcttcgtc ctttgcaaaa aaaaaaaaaa a 772

<210> 58

<211> 987

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 88..411

<220>

<221> sig_peptide

<222> 88..234

<223> Von Heijne matrix

score 4.70

seq LLLVSTWSADLMS/YR

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<222> 938..943

<220>

<221> polyA_site

<222> 964..987

<220>

<221> misc_feature

<222> 828,832

<223> n=a, g, c or t

<400> 58

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 ataatccagg cctgaatata tacaaat atg aac aag acc cac aag gac tgc tca 114

Met Asn Lys Thr His Lys Asp Cys Ser

-45

tca ccc cag tat tcc att tac aac atc ctg aat gaa ctc ccg acc agg 162
 Ser Pro Gln Tyr Ser Ile Tyr Asn Ile Leu Asn Glu Leu Pro Thr Arg

-40 -35 -30 -25

cct ata att ctc tct tgc agc caa ata tcc tgc tta ctc ctg gta tct 210
 Pro Ile Ile Leu Ser Cys Ser Gln Ile Ser Cys Leu Leu Leu Val Ser

-20 -15 -10

acc tgg tca gca gac ctc atg agt tat cgc cca gtg aca aaa cca tcc 258
 Thr Trp Ser Ala Asp Leu Met Ser Tyr Arg Pro Val Thr Lys Pro Ser

-5 1 5

caa aga tgc acc agt cca gca caa agt atg act gtc aat ctc aca aaa 306
 Gln Arg Cys Thr Ser Pro Ala Gln Ser Met Thr Val Asn Leu Thr Lys

10 15 20

gat gta ggg ttc tac gag gat act cag agt ata aga att acg cta agt 354
 Asp Val Gly Phe Tyr Glu Asp Thr Gln Ser Ile Arg Ile Thr Leu Ser

25 30 35 40

gaa ata agc caa gcc cag aaa gac aca tac ttt att att tca tgt atc 402
 Glu Ile Ser Gln Ala Gln Lys Asp Thr Tyr Phe Ile Ile Ser Cys Ile

45 50 55

tgt gga atc taaaagagtc aaattcatgg cagcagggag agggctgaag 451
 Cys Gly Ile

aagggggaga tggtgatcaa agtttctatg tatacaaaga ccaaaccatc acattatgcc 511

tcataaatat atacaattat tatttgctaa ttacaagtaa agcaatacaa gaagaaaaaa 571


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aggaatcata agtaaatcca tgacaagtga aaacgcaatg gagagaaggg aatcaatgat 631
tgaagaagag aaaggacagt ggatttacc aaacttcgaa agagtgatgt gactggcaaa 691
ggactgggga gaggtccttt gggaaatgga caaaaccctc gaatgggttag gaaagacaat 751
ctctttataa atgcggggca taagctgagc acaagggtgaa gtttggcatg tactgcctgt 811
ggatgttgta aaaattnatg ntcaaaagca aagcaattct tggttcatct gtgttcaactg 871
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<210> 59

<211> 1324

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 129..452

<220>

<221> sig_peptide

<222> 129..212

<223> Von Heijne matrix

score 5.20

seq LDIVISFVGAVSS/ST

<220>

<221> polyA_signal

<222> 1290..1295

<220>

<221> polyA_site

<222> 1309..1324

<220>

<221> misc_feature

<222> 888,1080

<223> n=a, g, c or t

<400> 59

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ctttcagtat tgaaaatact tactgttaat attcatgtaa gtaacaaaca tttaataaag 120
aaaaataa atg tat ttt cat ttt cta ggt gcc gga gca att ctt att cct 170
Met Tyr Phe His Phe Leu Gly Ala Gly Ala Ile Leu Ile Pro
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      -25      -20      -15
cgt tta gac att gtg att tcc ttc gtt gga gct gtg agc agc agc aca      218
Arg Leu Asp Ile Val Ile Ser Phe Val Gly Ala Val Ser Ser Ser Thr
      -10      -5      1
ttg gcc cta atc ctg cca cct ttg gtt gaa att ctt aca ttt tcg aag      266
Leu Ala Leu Ile Leu Pro Pro Leu Val Glu Ile Leu Thr Phe Ser Lys
      5      10      15
gaa cat tat aat ata tgg atg gtc ctg aaa aat att tct ata gca ttc      314
Glu His Tyr Asn Ile Trp Met Val Leu Lys Asn Ile Ser Ile Ala Phe
      20      25      30
act gga gtt gtt ggc ttc tta tta ggt aca tat ata act gtt gaa gaa      362
Thr Gly Val Val Gly Phe Leu Leu Gly Thr Tyr Ile Thr Val Glu Glu
      35      40      45      50
att att tat cct act ccc aaa gtt gta gct ggc act cca cag agt cct      410
Ile Ile Tyr Pro Thr Pro Lys Val Val Ala Gly Thr Pro Gln Ser Pro
      55      60      65
ttt cta aat ttg aat tca aca tgc tta aca tct ggt ttg aaa      452
Phe Leu Asn Leu Asn Ser Thr Cys Leu Thr Ser Gly Leu Lys
      70      75      80
tagtaaaagc agaatcatga gtcttctatt tttgtcccat ttctgaaaat tatcaagata      512
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gatattaata ttttggaagt aatcataact ctttaccagt agtggtaaac ctatgaaaaa      632
tccttgcttt taagtgttag caatagtcca aaaaattaag ttctgaaaat tgaaaaaatt      692
aaaatgtaaa aaaattaaag aataaaaaata cttctattat tcttttatct cagtaagaaa      752
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ttatgttttt attagccaaa ttctaagtat tggctcctgg aagtatagaa aactccatt      992
aacataatat aagcatcaga aaattgcaaa cactagaatt aattttacac tctaattgta      1052
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tgacaaggga ctttaaaact tatccagtgc aactcccttg tttttcgta gaggaaaagg      1172
aggcctagaa aggttaagta acttggtcga gaccactcag ccttgagatc aagaaaacct      1232
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<210> 60

<211> 1918

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 238..612

<220>

<221> sig_peptide

<222> 238..348

<223> Von Heijne matrix

score 9.40

seq LLCCVLSASQLSS/QD

<220>

<221> polyA_signal

<222> 1885..1890

<220>

<221> polyA_site

<222> 1905..1918

<220>

<221> misc_feature

<222> 945,1624

<223> n=a, g, c or t

<400> 60

aaaaatctaa gcgacttcga tgccaaggaa gttgtgtaaa tgtgcacgcg ctacaccaca	60
cccaggggtgg aaaccacagt tgcagagtca ttaaacaatc aattgtttgt ttaacatctg	120
tgataggcag ctttccttct tttcaacagt gatacctacg aaaatcaaaa taaatgcaag	180
ctgaggtttt gtgctcactg aaagggctgt caaccccaga aggccgacac aaaaaaa	237
atg gta tgt gaa gat gca ccg tct ttt caa atg gcc tgg gag agt caa	285
Met Val Cys Glu Asp Ala Pro Ser Phe Gln Met Ala Trp Glu Ser Gln	
-35 -30 -25	
atg gcc tgg gag agg ggg cct gcc ctt ctc tgc tgt gtc ctt tcg gct	333
Met Ala Trp Glu Arg Gly Pro Ala Leu Leu Cys Cys Val Leu Ser Ala	
-20 -15 -10	
tcc cag ttg agc tcc caa gac cag gac cca ctg ggg cat ata aaa tct	381
Ser Gln Leu Ser Ser Gln Asp Gln Asp Pro Leu Gly His Ile Lys Ser	
-5 1 5 10	
ctg ctg tat cct ttc ggc ttc cca gtt gag ctc cca aga cca gga ccc	429
Leu Leu Tyr Pro Phe Gly Phe Pro Val Glu Leu Pro Arg Pro Gly Pro	
15 20 25	
act ggg gca tat aaa aaa gtc aaa aat caa aat caa aca aca agt tct	477
Thr Gly Ala Tyr Lys Lys Val Lys Asn Gln Asn Gln Thr Thr Ser Ser	
30 35 40	

105

gag tta ctt agg aaa cag act tcg cat ttc aat cag aga ggc cac aga 525
 Glu Leu Leu Arg Lys Gln Thr Ser His Phe Asn Gln Arg Gly His Arg
 45 50 55
 gca agg tct aaa ctt ctg gct tct aga caa att cct gat aga aca ttt 573
 Ala Arg Ser Lys Leu Leu Ala Ser Arg Gln Ile Pro Asp Arg Thr Phe
 60 65 70 75
 aaa tgt ggg aag tgg ctt ccc cag gtc cca tcc cct gtt tagggataga 622
 Lys Cys Gly Lys Trp Leu Pro Gln Val Pro Ser Pro Val
 80 85
 gtgatatca tttttatagt tgccatgtat gcctctgect gaattttttt aattgacttt 682
 tgagcttttg agattgcacg agggagaaca aggcctttgc tgttggtgat aggaaagact 742
 taacctaaaa ttaaacacagc aagaaagcat tagtaaaaat ctaacaatat gaagggtctct 802
 tatgagtcac ttttttcaaa agatgaaaac tccagaaaacg cacaggaacg aaatacctcc 862
 cagaaacatg aagcaatcat cgaagactca ctggtaatat ttttaaaaag tatacagatc 922
 aaagcaaaaa gaagccatgt gtnaacaag agaaatgtgc aaatattttt taaggcagta 982
 ttaagtgcac gaggagtaac atgaaataaa cattctttca catggctact gggaatataa 1042
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 gggcaacacg gtgaaacccc gtctctacta aaatacaaaa aattagccgg gcgtcgcagc 1462
 atgcgcctgt agtcccagct gctcaggagg ctgaggcagg agaattgatt gaacccggga 1522
 ggcagagggt gactgagct gagattaagc caccgcactc cagcctgggc gacagagcaa 1582
 gattccgttc ccaagaaaaa aaaattgttc aacaataagg gncaaaggga gagaatcata 1642
 acatctgatt aaacagaaaa agcaagattt ttaaaactaa ctatataagg atggtcccag 1702
 ctgtgtcaaa aggaagcttg tttgtaatac gtgtgcataa aaattaaata gaggtgaaca 1762
 caattatttt aaggcagtta aattatctct gtattgtgaa ctaagacttt ctagaatttt 1822
 acttattcat tctgtactta aattttttct aatgaacaca tatacttttg taatcagaaa 1882
 atattaaatg catgtatttt tcaaaaaaaaa aaaaaa 1918

<210> 61

<211> 852

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 229..735

<220>

<221> sig_peptide
 <222> 229..492
 <223> Von Heijne matrix
 score 6.70
 seq VFALSSFLNKASA/VY

<220>
 <221> polyA_signal
 <222> 816..821

<220>
 <221> polyA_site
 <222> 841..852

<400> 61
 aatgactggc agtggcatca gcgatggcgg ctgcgtcggg gtcggttctg cagcgtgta 60
tcgtgtcgcc ggcagggagg catagcgctt ctctgatctt cctgcatggc tcaggtgatt 120
ctggacaagg attaagaatg tggatcaagc aggtttttaa atcaagattt aacattccaa 180
cacataaaaa ttatttatcc aacagctcct ccagatcat atactcct atg aaa gga 237
Met Lys Gly
gga atc tcc aat gta tgg ttt gac aga ttt aaa ata acc aat gac tgc 285
Gly Ile Ser Asn Val Trp Phe Asp Arg Phe Lys Ile Thr Asn Asp Cys
-85 -80 -75 -70
cca gaa cac ott gaa tca att gat gtc atg tgt caa gtg ctt act gat 333
Pro Glu His Leu Glu Ser Ile Asp Val Met Cys Gln Val Leu Thr Asp
-65 -60 -55
ttg att gat gaa gaa gta aaa agt ggc atc aag aag aac agg ata tta 381
Leu Ile Asp Glu Glu Val Lys Ser Gly Ile Lys Lys Asn Arg Ile Leu
-50 -45 -40
ata gga gga ttc tct atg gga gga tgc atg gca atg cat tta gca tat 429
Ile Gly Gly Phe Ser Met Gly Gly Cys Met Ala Met His Leu Ala Tyr
-35 -30 -25
aga aat cat caa gat gtg gca gga gta ttt gct ctt tct agt ttt ctg 477
Arg Asn His Gln Asp Val Ala Gly Val Phe Ala Leu Ser Ser Phe Leu
-20 -15 -10
aat aaa gca tct gct gtt tac cag gct ctt cag aag agt aat ggt gta 525
Asn Lys Ala Ser Ala Val Tyr Gln Ala Leu Gln Lys Ser Asn Gly Val
-5 1 5 10
ctt cct gaa tta ttt cag tgt cat ggt act gca gat gag tta gtt ctt 573
Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu Leu Val Leu
15 20 25
cat tct tgg gca gaa gag aca aac tca atg tta aaa tct cta gga gtg 621

107

His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser Leu Gly Val
30 35 40
acc acg aag ttt cat agt ttt cca aat gtt tac cat gag cta agc aaa 669
Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu Leu Ser Lys
45 50 55
act gag tta gac ata ttg aag tta tgg att ctt aca aag ctg cca gga 717
Thr Glu Leu Asp Ile Leu Lys Leu Trp Ile Leu Thr Lys Leu Pro Gly
60 65 70 75
gaa atg gaa aaa caa aaa tgaatgaatc aagagtgatt tgttaatgta 765
Glu Met Glu Lys Gln Lys
80
agtgtaatgt ctttgtgaaa agtgatTTTT actgccaaat tataatgata attaaaaatat 825
taagaaatag caaaaaaaaa aaaaaaa 852

<210> 62

<211> 726

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 168..413

<220>

<221> sig_peptide

<222> 168..335

<223> Von Heijne matrix

score 3.80

seq QMIMLVCFNLSRG/CL

<220>

<221> polyA_signal

<222> 684..689

<220>

<221> polyA_site

<222> 708..726

<220>

<221> misc_feature

<222> 723

<223> n=a, g, c or t

<400> 62

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cagcaaaatg gcaggaagg cagctctaag ctcccatcct tccataggaa tgttgaataa      60
acaaccagac actgtcagaa ccaactttgt gagaaccggg aaaataatca aaggtgtaag      120
gcaactaaaa gaatgctgga tcaacacaaa ggaaacttaa aaatgat atg aaa gct      176
                                     Met Lys Ala
                                     -55
gtg tgg cat ttt tgc ttg tcc cac aag tcc agc ttg gtg ata gtc ttg      224
Val Trp His Phe Cys Leu Ser His Lys Ser Ser Leu Val Ile Val Leu
                                     -50          -45          -40
aag acg gca ggc tgg att ccc cag gct ggg acc ctt atc cct ggt tcc      272
Lys Thr Ala Gly Trp Ile Pro Gln Ala Gly Thr Leu Ile Pro Gly Ser
                                     -35          -30          -25
aga gag gag agc aga tct gat tca caa atg att atg ctt gtc tgt ttt      320
Arg Glu Glu Ser Arg Ser Asp Ser Gln Met Ile Met Leu Val Cys Phe
                                     -20          -15          -10
aat ctt tcc aga ggc tgt ctg aag aag gta ttc atc atc tct gtt tta      368
Asn Leu Ser Arg Gly Cys Leu Lys Lys Val Phe Ile Ile Ser Val Leu
                                     -5           1           5           10
cct gac cca gaa acc att ctg cta gga aaa aca gtg ggc att gct      413
Pro Asp Pro Glu Thr Ile Leu Leu Gly Lys Thr Val Gly Ile Ala
                                     15           20           25
tgaaaacagt gttctgtggt tgaaaaaccc acagtcacct tgggctgggt ggaatgtaaa      473
atggcgccctc ttctggatca tcgtttggca gtttctcaaa aggtcaaacg tagaatcact      533
atttgatcca acaattctac tcctaggtat atccccaaaa gaattgaaaa caaggatgca      593
aacatatgcg tgtacactaa tgtttataga aaaaatattc acaataatca aaaggcagaa      653
acaacccaag tgtccaataa cagaagaatg aataaacagt gtgatataaa cataaaaaaa      713
aaaaaaaaaa aaa                                                    726

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<210> 63

<211> 1039

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 100..852

<220>

<221> sig_peptide

<222> 100..159

<223> Von Heijne matrix

score 6.10
seq FLILFLFLMECQL/HL

<220>

<221> polyA_signal

<222> 998..1003

<220>

<221> polyA_site

<222> 1019..1039

<400> 63

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agaacttctt gattcctcag ataaatagag gacagatgct ggactgtagc taagtatttc      60
ctttcatcta cgggataaaa tactgataat ttgagagtg atg gac aag gtt cag      114
                               Met Asp Lys Val Gln
                               -20
agt ggt ttc ctc att ttg ttt ttg ttt tta atg gaa tgc caa ctt cat      162
Ser Gly Phe Leu Ile Leu Phe Leu Phe Leu Met Glu Cys Gln Leu His
-15                -10                -5                1
tta tgc ttg ccg tat gca gat gga ctc cat ccc act gga aac ata aca      210
Leu Cys Leu Pro Tyr Ala Asp Gly Leu His Pro Thr Gly Asn Ile Thr
                5                10                15
ggc tta cca ggt agc ttc aac cac tgg ttt tat gtg act cag gga gaa      258
Gly Leu Pro Gly Ser Phe Asn His Trp Phe Tyr Val Thr Gln Gly Glu
                20                25                30
ttg aaa agc tgt ttc agg gga gat aaa aag aag gta att aca ttt cac      306
Leu Lys Ser Cys Phe Arg Gly Asp Lys Lys Lys Val Ile Thr Phe His
                35                40                45
cgc aaa aag ttt tct ttt caa ggc agt aaa cgg tca caa cca ccc aga      354
Arg Lys Lys Phe Ser Phe Gln Gly Ser Lys Arg Ser Gln Pro Pro Arg
50                55                60                65
aac atc acc aaa gag ccc aaa gtg ttc ttt cat aaa acc cag ttg cct      402
Asn Ile Thr Lys Glu Pro Lys Val Phe Phe His Lys Thr Gln Leu Pro
                70                75                80
ggg att caa ggg gct gcc tcg aga tcc acg gct gca tcc cct acg aac      450
Gly Ile Gln Gly Ala Ala Ser Arg Ser Thr Ala Ala Ser Pro Thr Asn
                85                90                95
ccc atg aaa ttc ctg agg aat aaa gca ata att cgg cat aga cct gct      498
Pro Met Lys Phe Leu Arg Asn Lys Ala Ile Ile Arg His Arg Pro Ala
                100                105                110
ctt gtt aaa gta att tta att tcg agc gta gcc ttc agc att gcc ctg      546
Leu Val Lys Val Ile Leu Ile Ser Ser Val Ala Phe Ser Ile Ala Leu

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110

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      115              120              125
ata tgt ggg atg gca atc tcc tat atg ata tat cga ctg gca cag gct      594
Ile Cys Gly Met Ala Ile Ser Tyr Met Ile Tyr Arg Leu Ala Gln Ala
130              135              140              145
gag gaa aga caa cag ctc gag tca ctt tat aag aac ctc agg ata ccg      642
Glu Glu Arg Gln Gln Leu Glu Ser Leu Tyr Lys Asn Leu Arg Ile Pro
      150              155              160
tta tta gga gat gaa gaa gag ggc tca gag gac gag ggt gag tcc acg      690
Leu Leu Gly Asp Glu Glu Glu Gly Ser Glu Asp Glu Gly Glu Ser Thr
      165              170              175
cac cta ctt cca aag aac gaa aat gag ctg gaa aag ttc atc cac tca      738
His Leu Leu Pro Lys Asn Glu Asn Glu Leu Glu Lys Phe Ile His Ser
      180              185              190
gtt att ata tca aaa aga agc aaa aat att aag aag aaa ctg aag gaa      786
Val Ile Ile Ser Lys Arg Ser Lys Asn Ile Lys Lys Lys Leu Lys Glu
      195              200              205
gag caa aac tca gta aca gaa aac aaa aca aag aat gcg tca cat aat      834
Glu Gln Asn Ser Val Thr Glu Asn Lys Thr Lys Asn Ala Ser His Asn
210              215              220              225
gga aaa atg gaa gac ttg tgaacgcaga cgacagaggt gccggctgag      882
Gly Lys Met Glu Asp Leu
      230
gcagaggaga aactatgggg gtgctgggag actgagcctg tgggcgtggc ttgctcccag      942
agaaccttat ggaagaggac atcaaagaaa gaaatgccag acctgtatcc cagaaaataa      1002
agccacatga tatagcaaaa aaaaaaaaaa aaaaaaa      1039

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<210> 64

<211> 1355

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 238..1152

<220>

<221> sig_peptide

<222> 238..339

<223> Von Heijne matrix

score 8.50

seq SIFLLLSFPDSNG/KA

<220>

<221> polyA_signal

<222> 1298..1303

<220>

<221> polyA_site

<222> 1324..1355

<400> 64

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aattttcttg aaatcacatg gtaccaatca caagtcttgt tattttgttt cattatgaga      60
aagataatct actaaatatt aaaatactgg aaggagcaag atagctttga tccagggaga      120
ccttttccat ttatgtgctt tagtaatctg ccgccaacaa gctatcttct ttatgttctt      180
ctacaactga tgttggtttg ttttctcatg tttgtctctt aatagacaaa tggagggc      237
atg agc ttc ctt aga att acc cct tcg acg cat agt tct gtt tca tct      285
Met Ser Phe Leu Arg Ile Thr Pro Ser Thr His Ser Ser Val Ser Ser
      -30              -25              -20
gga ctt ttg agg ctt agt atc ttt cta cta ctt agc ttt cct gac tca      333
Gly Leu Leu Arg Leu Ser Ile Phe Leu Leu Leu Ser Phe Pro Asp Ser
      -15              -10              -5
aac gga aaa gcc att tgg aca gct cac ctg aat ata aca ttt cag gtt      381
Asn Gly Lys Ala Ile Trp Thr Ala His Leu Asn Ile Thr Phe Gln Val
      1              5              10
gga aat gag atc aca tcg gaa tta gga gag agt gga gtg ttc ggg aat      429
Gly Asn Glu Ile Thr Ser Glu Leu Gly Glu Ser Gly Val Phe Gly Asn
      15              20              25              30
cat tct cct ctg gaa agg gtg tct ggt gtg gtg gca ctt cct gaa gaa      477
His Ser Pro Leu Glu Arg Val Ser Gly Val Val Ala Leu Pro Glu Glu
      35              40              45
tgg aat cag aat gcc tgt cat cct ttg acc aat ttc agc agg ccc aaa      525
Trp Asn Gln Asn Ala Cys His Pro Leu Thr Asn Phe Ser Arg Pro Lys
      50              55              60
cag gca gac tca tgg ctg gcc ctc atc gaa cgt gga ggc tgt act ttt      573
Gln Ala Asp Ser Trp Leu Ala Leu Ile Glu Arg Gly Gly Cys Thr Phe
      65              70              75
aca cat aaa atc aac gtg gca gca gag aag gga gca aat ggg gtg atc      621
Thr His Lys Ile Asn Val Ala Ala Glu Lys Gly Ala Asn Gly Val Ile
      80              85              90
atc tac aac tat caa ggt acg ggc agt aaa gta ttt ccc atg tct cac      669
Ile Tyr Asn Tyr Gln Gly Thr Gly Ser Lys Val Phe Pro Met Ser His
      95              100              105              110
cag ggg acg gaa aat ata gtc gcg gtg atg ata agc aac ctg aaa ggc      717
Gln Gly Thr Glu Asn Ile Val Ala Val Met Ile Ser Asn Leu Lys Gly

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                                112
                                115      120      125
atg gaa att ttg cac tgc att cag aaa gga gtc tat gtg aca gtc atc      765
Met Glu Ile Leu His Ser Ile Gln Lys Gly Val Tyr Val Thr Val Ile
                                130      135      140
att gaa gtg ggg aga atg cac atg cag tgg gtg agc cat tac atc atg      813
Ile Glu Val Gly Arg Met His Met Gln Trp Val Ser His Tyr Ile Met
                                145      150      155
tat cta ttt acc ttc ctg gct gcc aca att gcc tac ttt tac tta gat      861
Tyr Leu Phe Thr Phe Leu Ala Ala Thr Ile Ala Tyr Phe Tyr Leu Asp
                                160      165      170
tgc gtc tgg aga ctt aca cct aga gtg ccc aat tct ttc acc agg agg      909
Cys Val Trp Arg Leu Thr Pro Arg Val Pro Asn Ser Phe Thr Arg Arg
                                175      180      185      190
cga agt caa ata aag aca gat gtg aag aaa gct att gac cag ctt caa      957
Arg Ser Gln Ile Lys Thr Asp Val Lys Lys Ala Ile Asp Gln Leu Gln
                                195      200      205
ctg cga gtt ctc aaa gaa ggg gat gag gaa tta gac cta aat gaa gac      1005
Leu Arg Val Leu Lys Glu Gly Asp Glu Glu Leu Asp Leu Asn Glu Asp
                                210      215      220
aac tgt gtt gtt tgc ttt gac aca tac aaa ccc caa gat gta gta cgc      1053
Asn Cys Val Val Cys Phe Asp Thr Tyr Lys Pro Gln Asp Val Val Arg
                                225      230      235
att tta act tgc aaa cat ttt ttc cat aag gca tgc att gac ccc tgg      1101
Ile Leu Thr Cys Lys His Phe Phe His Lys Ala Cys Ile Asp Pro Trp
                                240      245      250
ctt tta gcc cat agg aca tgt ccc atg tgc aag tgt gac atc ctg aaa      1149
Leu Leu Ala His Arg Thr Cys Pro Met Cys Lys Cys Asp Ile Leu Lys
                                255      260      265      270
act taagaaatct ggagaatttt ctgaagatgt aaccagatct ttccaaatac      1202
Thr
aaagattaga taaattgtct tattgtactt tatgtagaga gaaaatttca gcttctctac      1262
ccaagtatga acaagggtga aatttgtgtt ttaaaaataa aactccttat catgcccagc      1322
taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa      1355

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<210> 65

<211> 572

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 187..369

<220>
 <221> sig_peptide
 <222> 187..312
 <223> Von Heijne matrix
 score 7.10
 seq LLPCSSVLTCGQA/SQ

<220>
 <221> polyA_signal
 <222> 489..494

<220>
 <221> polyA_site
 <222> 558..572

<220>
 <221> misc_feature
 <222> 94,527,537..538
 <223> n=a, g, c or t

<400> 65
 cttcttcagt cagtggctgg ataatctaata tataatgtta taatccatca tttctctttt 60
 tgaacagtca atttagttta acatttgctt aacnagccat tatgtatgcc aggtaatgtg 120
 ctagatgctg gtggttcaaa gaaaggaacg atgtggacct gacctcaaag aaatccattg 180
 gagaat atg aca gat tta gat tta atg atc aac ttt act ttt cct ata 228
 Met Thr Asp Leu Asp Leu Met Ile Asn Phe Thr Phe Pro Ile
 -40 -35 -30
 cag tgg gtc aac caa aac cgc atg gcg tac tac tct ctg aag cct cta 276
 Gln Trp Val Asn Gln Asn Arg Met Ala Tyr Tyr Ser Leu Lys Pro Leu
 -25 -20 -15
 cta ccc tgc tcc tcc gtg ttg aca tgt ggt cag gca agc cag gac tta 324
 Leu Pro Cys Ser Ser Val Leu Thr Cys Gly Gln Ala Ser Gln Asp Leu
 -10 -5 1
 ctc aca tca gct aca tca gtt act ggg atg gag aaa att gaa gcc 369
 Leu Thr Ser Ala Thr Ser Val Thr Gly Met Glu Lys Ile Glu Ala
 5 10 15
 tagaaagatc aagaaacttt ctccaggcca taaatagagg aatcaggatt caaatcagat 429
 agaccccagg gcttgttctc ttcaacacca cattacccta cattattatt caattattaa 489
 ataaaaacctt gcattagtgg catttccaaa tgcataanca aaaaaatnna aaaaaaagta 549
 aactggcaa aaaaaaaaaa aaa 572

<210> 66
 <211> 535
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> 121..459

<220>
 <221> sig_peptide
 <222> 121..165
 <223> Von Heijne matrix
 score 4.20
 seq FYLLASSILCAL/IV

<220>
 <221> polyA_signal
 <222> 497..502

<220>
 <221> polyA_site
 <222> 521..535

<220>
 <221> misc_feature
 <222> 486,489
 <223> n=a, g, c or t

<400> 66
 agttacacca ggcacccctgg cccaaagttt cccaaatcca ggcggctaga ggcccactgc 60
 ttcccaacta ccagctgagg gggcccgtec cgagaagga gaagaggccg aagaggaaac 120
 atg aac ttc tat tta ctc cta gcg agc agc att ctg tgt gcc ttg att 168
 Met Asn Phe Tyr Leu Leu Leu Ala Ser Ser Ile Leu Cys Ala Leu Ile
 -15 -10 -5 1
 gtc ttc tgg aaa tat cgc cgc ttt cag aga aac act ggc gaa atg tca 216
 Val Phe Trp Lys Tyr Arg Arg Phe Gln Arg Asn Thr Gly Glu Met Ser
 5 10 15
 tca aat tca act gct ctt gca cta gtg aga ccc tct tct tct ggg tta 264
 Ser Asn Ser Thr Ala Leu Ala Leu Val Arg Pro Ser Ser Ser Gly Leu
 20 25 30
 att aac agc aat aca gac aac aat ctt gca gtc tac gac ctc tct cgg 312

115

Ile Asn Ser Asn Thr Asp Asn Asn Leu Ala Val Tyr Asp Leu Ser Arg
35 40 45
gat att tta aat aat ttc cca cac tca ata gcc agg cag aag cga ata 360
Asp Ile Leu Asn Asn Phe Pro His Ser Ile Ala Arg Gln Lys Arg Ile
50 55 60 65
ttg gta aac ctc agt atg gtg gaa aac aag ctg gtt gaa ctg gaa cat 408
Leu Val Asn Leu Ser Met Val Glu Asn Lys Leu Val Glu Leu Glu His
70 75 80
act cta ctt agc aag ggt ttc aga ggt gca tca cct cac cgg aaa tcc 456
Thr Leu Leu Ser Lys Gly Phe Arg Gly Ala Ser Pro His Arg Lys Ser
85 90 95
acc taaaagcgta caggatgtaa tgccagnngn ggaaatcatt aaagacactt 509
Thr
tgagtagatt caaaaaaaaa aaaaaa 535

<210> 67

<211> 572

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 34..336

<220>

<221> sig_peptide

<222> 34..123

<223> Von Heijne matrix

score 7.80

seq SVTLAQLQLVQQ/GQ

<220>

<221> polyA_signal

<222> 536..541

<220>

<221> polyA_site

<222> 556..572

<220>

<221> misc_feature

<222> 545

<223> n=a, g, c or t

<400> 67

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gcattacacg ccggtcagga ttccgcgaccc gac atg gag cgt ccc cgc agt ccc      54
                               Met Glu Arg Pro Arg Ser Pro
                               -30      -25

caa tgc tgc gcc ccg gcc tct gcc tca gct tgc gtt acc ctg gcg cag      102
Gln Cys Ser Ala Pro Ala Ser Ala Ser Ala Ser Val Thr Leu Ala Gln
          -20      -15      -10

ctc ctg cag ctg gtc cag cag gcc cag gaa ctc ccg gcc ctg gag aaa      150
Leu Leu Gln Leu Val Gln Gln Gly Gln Glu Leu Pro Gly Leu Glu Lys
          -5      1      5

cgc cac atc gcg gcg atc cac gcc gaa ccc aca gcg tcc cgg ctg ccg      198
Arg His Ile Ala Ala Ile His Gly Glu Pro Thr Ala Ser Arg Leu Pro
10      15      20      25

cgg agg ccc aag ccc tgg gag gcc gcg gct ttg gct gag tcc ctt ccc      246
Arg Arg Pro Lys Pro Trp Glu Ala Ala Ala Leu Ala Glu Ser Leu Pro
          30      35      40

cct ccg acc ctc agg ata gga acg gcc ccg gcg gag cct gcc ttg gtt      294
Pro Pro Thr Leu Arg Ile Gly Thr Ala Pro Ala Glu Pro Gly Leu Val
          45      50      55

gag gca gcg act gcg cct tct tca tgg cat aca gtg gcc ccc      336
Glu Ala Ala Thr Ala Pro Ser Ser Trp His Thr Val Gly Pro
          60      65      70

tgagggttcca ggtcctttgc ggcggcgatc tggagggcgt ggctacagga cccgggatgc      396
cattcagtta ctcatctttt atgctttcgt cctgacctgt ctcaactaga cttgctcctg      456
caaccacat ggggggttttg catttacatt tgtggaccat gttacagtta agaaaaatcc      516
tgtttcagtc cttatatgta ataaaatgnt ttatgatgca aaaaaaaaaa aaaaaa      572

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<210> 68

<211> 804

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 119..409

<220>

<221> sig_peptide

<222> 119..388

<223> Von Heijne matrix

score 4.30
seq TCLTACWTALCCC/CL

<220>

<221> polyA_signal

<222> 769..774

<220>

<221> polyA_site

<222> 789..804

<220>

<221> misc_feature

<222> 274

<223> n=a, g, c or t

<220>

<221> unsure

<222> -39

<223> Xaa = His,Gln

<400> 68

acttgctctg agacaggtgc ggcaagtcta ctgcgggctg gtccgggctc ctcaggttca	60
gaccgcaccg ttatccagtc ggttcgtgga gaggagaggt gcactttaca ggtcccca	118
atg aac caa gag aac cct cca cca tat cca ggc cct ggt cca acg gcc	166
Met Asn Gln Glu Asn Pro Pro Pro Tyr Pro Gly Pro Gly Pro Thr Ala	
-90 -85 -80 -75	
cca tac cca cct tat cca cca caa cca atg ggt cca gga cct atg ggg	214
Pro Tyr Pro Pro Tyr Pro Pro Gln Pro Met Gly Pro Gly Pro Met Gly	
-70 -65 -60	
gga ccc tac cca cct cct caa ggg tac ccc tac caa gga tac cta cag	262
Gly Pro Tyr Pro Pro Pro Gln Gly Tyr Pro Tyr Gln Gly Tyr Leu Gln	
-55 -50 -45	
tac ggc tgg can ggt gga cct cag gag cct cct aaa acc aca gtg tat	310
Tyr Gly Trp Xaa Gly Gly Pro Gln Glu Pro Pro Lys Thr Thr Val Tyr	
-40 -35 -30	
gtg gta gaa gac caa aga aga gat gag cta gga cca tcc acc tgc ctc	358
Val Val Glu Asp Gln Arg Arg Asp Glu Leu Gly Pro Ser Thr Cys Leu	
-25 -20 -15	
aca gcc tgc tgg acg gct ctc tgt tgc tgc tgt ctc tgg gac atg ctc	406
Thr Ala Cys Trp Thr Ala Leu Cys Cys Cys Leu Trp Asp Met Leu	
-10 -5 1 5	


```

acc tgaccagacc agcccagccg tctgtctctg ccagctctgc tgccacctct      459
Thr
gacagggtgtg cctgccccca tctcttctga ttgctgttaa caaatgacta gctttgcaca      519
gacacctcta ccttcagcac tatgggattc tagattaatg ggggttgcta ctgtttaatt      579
cagtgacttg atctttttta tgcctaaaat ccatttctta ttgatcttta aagatgtgct      639
aaatgacttt tttggccaaa ggcttagttg tgaaaaatat aattttttaa ttatacatc      699
aaggtagtgg ccaaagttaa cacatcaatc atggaatgat ttctctgcta acagccgcct      759
gtatgtttca ataaatttgt ccaaagctca aaaaaaaaaa aaaaaa      804

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<210> 69

<211> 629

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 232..534

<220>

<221> sig_peptide

<222> 232..306

<223> Von Heijne matrix

score 3.70

seq AKTCLVLCRVLS/VI

<220>

<221> polyA_signal

<222> 595..600

<220>

<221> polyA_site

<222> 615..629

<400> 69

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tatcactggt acgaaccaag gatttacaga tcaactggcaa aaattctgag aactttcaca      60
ccagtatact gtccaagccc attaagtggc atcacacctc tcttttatgt agctcagaca      120
agacagtcta atatcttcaa aatactactg caatatggaa tcttagaaag agaaaaaac      180
cctatcaaca ttgtcttaac aatagtactc tacccttcga gagtaagagt a atg gtt      237
                                     Met Val
                                     -25
gat cgt gaa ttg gct gac atc cat gaa gat gcc aaa aca tgt ttg gta      285
Asp Arg Glu Leu Ala Asp Ile His Glu Asp Ala Lys Thr Cys Leu Val

```

-20 -15 -10
cta tgt tcc aga gtg ctt tct gtc att tca gtc aag gaa ata aag aca 333
Leu Cys Ser Arg Val Leu Ser Val Ile Ser Val Lys Glu Ile Lys Thr
-5 1 5
cag ctg agt tta gga aga cat cca att att tca aat tgg ttt gat tac 381
Gln Leu Ser Leu Gly Arg His Pro Ile Ile Ser Asn Trp Phe Asp Tyr
10 15 20 25
att cct tca aca aga tac aaa gat cca tgt gaa cta tta cat ctt tgc 429
Ile Pro Ser Thr Arg Tyr Lys Asp Pro Cys Glu Leu Leu His Leu Cys
30 35 40
aga cta acc atc agg aat caa cta tta acc aac aat atg ctc cca gat 477
Arg Leu Thr Ile Arg Asn Gln Leu Leu Thr Asn Asn Met Leu Pro Asp
45 50 55
gga ata ttt tca ctt cta att cct gct cgt cta caa aac tat ctg aat 525
Gly Ile Phe Ser Leu Leu Ile Pro Ala Arg Leu Gln Asn Tyr Leu Asn
60 65 70
tta gaa atc taacatacgt cagtgtccta agttccttaa caatgcttac 574
Leu Glu Ile
75
caatgtatgg cttagaagtt aataaaaatt cacttcatgc aaaaaaaaaa aaaaa 629

<210> 70

<211> 669

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 140..595

<220>

<221> sig_peptide

<222> 140..442

<223> Von Heijne matrix

score 4.10

seq VFMLIVSVLALIP/ET

<220>

<221> polyA_signal

<222> 630..635

<220>

<221> polyA_site

<222> 655..669

<400> 70

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gagcgggaag ccgagctggg cgagaagtag gggagggcgg tgctccgccg cggaggcggt    60
tgctatcgct tcgcagaacc tactcaggca gccagctgag aagagttgag ggattgctgc    120
tgctgggtct gcagacgcg atg gat aac gtg cag ccg aaa ata aaa cat cgc    172
               Met Asp Asn Val Gln Pro Lys Ile Lys His Arg
               -100               -95
ccc ttc tgc ttc agt gtg aaa ggc cac gtg aag atg ctg cgg ctg gca    220
Pro Phe Cys Phe Ser Val Lys Gly His Val Lys Met Leu Arg Leu Ala
-90               -85               -80               -75
cta act gtg aca tct atg acc ttt ttt atc atc gca caa gcc cct gaa    268
Leu Thr Val Thr Ser Met Thr Phe Phe Ile Ile Ala Gln Ala Pro Glu
               -70               -65               -60
cca tat att gtt atc act gga ttt gaa gtc acc gtt atc tta ttt ttc    316
Pro Tyr Ile Val Ile Thr Gly Phe Glu Val Thr Val Ile Leu Phe Phe
               -55               -50               -45
ata ctt tta tat gta ctc aga ctt gat cga tta atg aag tgg tta ttt    364
Ile Leu Leu Tyr Val Leu Arg Leu Asp Arg Leu Met Lys Trp Leu Phe
               -40               -35               -30
tgg cct ttg ctt gat att atc aac tca ctg gta aca aca gta ttc atg    412
Trp Pro Leu Leu Asp Ile Ile Asn Ser Leu Val Thr Thr Val Phe Met
               -25               -20               -15
ctc atc gta tct gtg ttg gca ctg ata cca gaa acc aca aca ttg aca    460
Leu Ile Val Ser Val Leu Ala Leu Ile Pro Glu Thr Thr Thr Leu Thr
-10               -5               1               5
gtt ggt gga ggg gtg ttt gca ctt gtg aca gca gta tgc tgt ctt gcc    508
Val Gly Gly Gly Val Phe Ala Leu Val Thr Ala Val Cys Cys Leu Ala
               10               15               20
gac ggg gcc ctt att tac cgg aag ctt ctg ttc aat ccc agc ggt cct    556
Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn Pro Ser Gly Pro
               25               30               35
tac cag aaa aag cct gtg cat gaa aaa aaa gaa gtt ttg taattttata    605
Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu
               40               45               50
ttacttttta gtttgatact aagtattaaa catatttctg tattottcca aaaaaaaaaa    665
aaaaa                                              669

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<210> 71

<211> 973

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 32..658

<220>

<221> sig_peptide

<222> 32..289

<223> Von Heijne matrix

score 4.00

seq KLWKLLFLMKSQG/WI

<220>

<221> polyA_signal

<222> 936..941

<220>

<221> polyA_site

<222> 959..973

<220>

<221> misc_feature

<222> 934

<223> n=a, g, c or t

<400> 71

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aggagagagg atggctagtg aggttttagat c atg ttg agc cct acc ttt gtt      52
                               Met Leu Ser Pro Thr Phe Val
                               -85                -80
ttg tgg gat gtt gga tat ccc tta tac acc tat gga tcc atc tgc att      100
Leu Trp Asp Val Gly Tyr Pro Leu Tyr Thr Tyr Gly Ser Ile Cys Ile
                               -75                -70                -65
att gca tta att att tgg caa gtg aaa aag agc tgc caa aaa tta agc      148
Ile Ala Leu Ile Ile Trp Gln Val Lys Lys Ser Cys Gln Lys Leu Ser
                               -60                -55                -50
ttg gta cct aac agg agc tgt tgc cgg tgt cac cga aga gtc caa caa      196
Leu Val Pro Asn Arg Ser Cys Cys Arg Cys His Arg Arg Val Gln Gln
                               -45                -40                -35
aag tct gga gat aga aca tca aga gct agg aga act tca cag gaa gaa      244
Lys Ser Gly Asp Arg Thr Ser Arg Ala Arg Arg Thr Ser Gln Glu Glu
                               -30                -25                -20

```

122

```

gcc gag aag ttg tgg aag ctg ctg ttt ctc atg aaa agc cag ggc tgg      292
Ala Glu Lys Leu Trp Lys Leu Leu Phe Leu Met Lys Ser Gln Gly Trp
-15              -10              -5              1
att cct cag gaa gga agt gtg cgg cga atc ctg tgt gca gac ccc tgc      340
Ile Pro Gln Glu Gly Ser Val Arg Arg Ile Leu Cys Ala Asp Pro Cys
          5              10              15
tgc caa atc tgc aat gtt atg gct ctg gag att aag caa ttg ctg gca      388
Cys Gln Ile Cys Asn Val Met Ala Leu Glu Ile Lys Gln Leu Leu Ala
          20              25              30
gaa gct cca gaa gtt ggc ttg gat aac aag atg aag ctg ttt ctg cac      436
Glu Ala Pro Glu Val Gly Leu Asp Asn Lys Met Lys Leu Phe Leu His
          35              40              45
tgg att aac cct gaa atg aaa gat cga agg cat gag gaa tcc att ctc      484
Trp Ile Asn Pro Glu Met Lys Asp Arg Arg His Glu Glu Ser Ile Leu
50              55              60              65
ctt tct aag gct gag aca gtg acc caa gac agg aca aaa aac att gag      532
Leu Ser Lys Ala Glu Thr Val Thr Gln Asp Arg Thr Lys Asn Ile Glu
          70              75              80
aag agt cca act gtc acc aaa gat cat gtg tgg gga gct aca aca cag      580
Lys Ser Pro Thr Val Thr Lys Asp His Val Trp Gly Ala Thr Thr Gln
          85              90              95
aag aca aca gag gac cct gag gct cag cct cct tct act gag gag gaa      628
Lys Thr Thr Glu Asp Pro Glu Ala Gln Pro Pro Ser Thr Glu Glu Glu
          100              105              110
ggc ctg atc ttc tgt gat gcc ccc agt gcc taaataatct gctctagcaa      678
Gly Leu Ile Phe Cys Asp Ala Pro Ser Ala
          115              120
cactcccttc agtcagcca atcctgggtc ctgtgccact cctacaaatg ctccaaactc      738
tgtcctcaaa tgacttgtgc cactcaacca ggaaatctat ccaggtcta actcacctca      798
gcagaaggca ctgttttatg caagaatacc catcacaaga aaaaggagtt cataggttcc      858
tgaacctctg caatcccctg aaaaaggctt tcattgccat ttccattaac atgcaggtga      918
agcagggcac tctccnaaat atactttgta cctttaagct aaaaaaaaaa aaaaa      973

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<210> 72

<211> 791

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> 14..280

<220>

<221> sig_peptide

<222> 14..76

<223> Von Heijne matrix

score 9.50

seq ALVVLCAPQLVAA/LE

<220>

<221> polyA_site

<222> 776..791

<220>

<221> misc_feature

<222> 607

<223> n=a, g, c or t

<400> 72

ataggcgcgc acc atg ggc tcc tgc tcc ggc cgc tgc gcg ctc gtc gtc	49
Met Gly Ser Cys Ser Gly Arg Cys Ala Leu Val Val	
-20 -15 -10	
ctc tgc gct ttt cag ctg gtc gcc gcc ctg gag agg cag gtg ttt gac	97
Leu Cys Ala Phe Gln Leu Val Ala Ala Leu Glu Arg Gln Val Phe Asp	
-5 1 5	
ttc ctg ggc tac cag tgg gcg ccc atc ctg gcc aac ttt gtc cac atc	145
Phe Leu Gly Tyr Gln Trp Ala Pro Ile Leu Ala Asn Phe Val His Ile	
10 15 20	
atc atc gtc atc ctg gga ctc ttc ggc acc atc cag tac cgg ctg cgc	193
Ile Ile Val Ile Leu Gly Leu Phe Gly Thr Ile Gln Tyr Arg Leu Arg	
25 30 35	
tat gtc atg tgt aca cgc tgt ggg cag ccg tct ggg tca cct gga acg	241
Tyr Val Met Cys Thr Arg Cys Gly Gln Pro Ser Gly Ser Pro Gly Thr	
40 45 50 55	
tct tca tca tct gct tct acc tgg aag tgg gtc gcc tct taaaggacag	290
Ser Ser Ser Ser Ala Ser Thr Trp Lys Ser Val Ala Ser	
60 65	
cgagctactg accttcagcc tctcccgcca tcgctcctgg tggcgtgagc gctggccagg	350
ctgtctgcat gaggaggtgc cagcagtggg cctcggggcc ccccatggcc aggcctggt	410
gtcaggtgct ggctgtgcca tggagccag ctatgtggag gccctacaca gttgcctgca	470
gatectgac gcgcttctgg gctttgtctg tggctgccag gtggtcagcg tgtttacgga	530
ggaagaggac agctgcctgc gtaagtgagg aaacagctga tctgctcct gtggcctcca	590
gcctcagcga ccgaccnagt gacaatgaca ggagctccca ggcttgga cgcgccccca	650
cccagcacc cccaggcggc cggcagcacc tgcctgggt tetaagtact ggacaccagc	710

cagggcgcca gggcagtgcc acggctggct gcagcgtcaa gagagtttgt aatttccttt 770
 ctcttaaaaa aaaaaaaaaa a 791

<210> 73
 <211> 1110
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> 93..290

<220>
 <221> sig_peptide
 <222> 93..149
 <223> Von Heijne matrix
 score 9.30
 seq VFVFLFLWDPVLA/GI

<220>
 <221> polyA_signal
 <222> 1078..1083

<220>
 <221> polyA_site
 <222> 1096..1110

<400> 73
 agtataggac tgtgtgctca acctcttctc totgttccct gacagccgat gtcagaccct 60
 gccactagcc tccttaacag aagttcccag cc atg aag cct ctc ctt gtt gtg 113
 Met Lys Pro Leu Leu Val Val
 -15
 ttt gtc ttt ctt ttc ctt tgg gat cca gtg ctg gca ggt ata aat tca 161
 Phe Val Phe Leu Phe Leu Trp Asp Pro Val Leu Ala Gly Ile Asn Ser
 -10 -5 1
 tta tca tca gaa atg cac aag aaa tgc tat aaa aat ggc atc tgc aga 209
 Leu Ser Ser Glu Met His Lys Lys Cys Tyr Lys Asn Gly Ile Cys Arg
 5 10 15 20
 ctt gaa tgc tat gag agt gaa atg tta gtt gcc tac tgt atg ttt cag 257
 Leu Glu Cys Tyr Glu Ser Glu Met Leu Val Ala Tyr Cys Met Phe Gln
 25 30 35
 ctg gag tgc tgt gtc aaa gga aat cct gca ccc tgacataaga aaccaatgaa 310

125

Leu Glu Cys Cys Val Lys Gly Asn Pro Ala Pro

40	45	
tggccactat	cctgtaggcc	cttgattctg ccattcttca caaaaccagg gaatttagat 370
caaactgtga	caccatgatg	tgtccatgac tactgggttt tagcattttt ataggccagc 430
agactcttgt	ggtctttaa	ttaaagagct gagctgtagc cttctttaa agagctcgg 490
ttttcacaaa	aacaatgtag	aagatatttt ctcacctcaa cgtgatgtcc agtgtgctca 550
tcagcacctg	tttctccctc	taatcataga ggatattctt attatttaga aaggcttcaa 610
gggaaacaac	ttttgacacc	taagtcgtgt cctaccttcg cttcagcttc gcatttccca 670
tttctgtgaa	attcccaaca	gagaagcaga tttgccatgg cttcttgaca accttgata 730
tctctcacat	aaaccgcata	ggcagggctt gactacaggc tggcccgagt ctgcactgag 790
tctgaccctg	aagttccctt	ggaacaggag aggccatctt gtgatgggct ggaacaaggt 850
aatttctcat	ccacctccct	agtttcagtt gagcaatgga acttcccacc tgagcccta 910
gggttcagct	acaggtata	agactgccgt cctgtgggtt agtgttggtt ccttagcagc 970
agagtgatgc	cacctctgct	gcccgatcgc tgactcctct ggatgggtgt tatcctgtgg 1030
cttaagagct	aacaccatgc	tgatcttgct ttgctatatg tgtaactaat aaactgccta 1090
aatccaaaaa	aaaaaaaaaa	1110

<210> 74

<211> 325

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -26...-1

<400> 74

Met	Ala	Thr	Pro	Leu	Pro	Pro	Pro	Ser	Pro	Arg	His	Leu	Arg	Leu	Leu
-25					-20						-15				
Arg	Leu	Leu	Leu	Ser	Gly	Leu	Val	Leu	Gly	Ala	Ala	Leu	Arg	Gly	Ala
-10				-5					1				5		
Ala	Ala	Gly	His	Pro	Asp	Val	Ala	Ala	Cys	Pro	Gly	Ser	Leu	Asp	Cys
	10					15					20				
Ala	Leu	Lys	Arg	Arg	Ala	Arg	Cys	Pro	Pro	Gly	Ala	His	Ala	Cys	Gly
25					30					35					
Pro	Cys	Leu	Gln	Pro	Phe	Gln	Glu	Asp	Gln	Gln	Gly	Leu	Cys	Val	Pro
40					45					50					
Arg	Met	Arg	Arg	Pro	Pro	Gly	Gly	Gly	Arg	Pro	Gln	Pro	Arg	Leu	Glu
55				60					65					70	
Asp	Glu	Ile	Asp	Phe	Leu	Ala	Gln	Glu	Leu	Ala	Arg	Lys	Glu	Ser	Gly
		75					80						85		
His	Ser	Thr	Pro	Pro	Leu	Pro	Lys	Asp	Arg	Gln	Arg	Leu	Pro	Glu	Pro

126

90	95	100
Ala Thr Leu Gly Phe Ser Ala Arg Gly Gln Gly Leu Glu Leu Gly Leu		
105	110	115
Pro Ser Thr Pro Gly Thr Pro Thr Pro Thr Pro His Thr Ser Leu Gly		
120	125	130
Ser Pro Val Ser Ser Asp Pro Val His Met Ser Pro Leu Glu Pro Arg		
135	140	145
Gly Gly Gln Gly Asp Gly Leu Ala Leu Val Leu Ile Leu Ala Phe Cys		
155	160	165
Val Ala Gly Ala Ala Ala Leu Ser Val Ala Ser Leu Cys Trp Cys Arg		
170	175	180
Leu Gln Arg Glu Ile Arg Leu Thr Gln Lys Ala Asp Tyr Ala Thr Ala		
185	190	195
Lys Ala Pro Gly Ser Pro Ala Ala Pro Arg Ile Ser Pro Gly Asp Gln		
200	205	210
Arg Leu Ala Gln Ser Ala Glu Met Tyr His Tyr Gln His Gln Arg Gln		
215	220	225
Gln Met Leu Cys Leu Glu Arg His Lys Glu Pro Pro Lys Glu Leu Asp		
235	240	245
Thr Ala Ser Ser Asp Glu Glu Asn Glu Asp Gly Asp Phe Thr Val Tyr		
250	255	260
Glu Cys Pro Gly Leu Ala Pro Thr Gly Glu Met Glu Val Arg Asn Pro		
265	270	275
Leu Phe Asp His Ala Ala Leu Ser Ala Pro Leu Pro Ala Pro Ser Ser		
280	285	290
Pro Pro Ala Leu Pro		
295		

<210> 75

<211> 302

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 75

Met Lys Ala Pro Gly Arg Leu Val Leu Ile Ile Leu Cys Ser Val Val

-15

-10

-5

Phe Ser Ala Val Tyr Ile Leu Leu Cys Cys Trp Ala Gly Leu Pro Leu

1

5

10

127

Cys Leu Ala Thr Cys Leu Asp His His Phe Pro Thr Gly Ser Arg Pro
 15 20 25 30
 Thr Val Pro Gly Pro Leu His Phe Ser Gly Tyr Ser Ser Val Pro Asp
 35 40 45
 Gly Lys Pro Leu Val Arg Glu Pro Cys Arg Ser Cys Ala Val Val Ser
 50 55 60
 Ser Ser Gly Gln Met Leu Gly Ser Gly Leu Gly Ala Glu Ile Asp Ser
 65 70 75
 Ala Glu Cys Val Phe Arg Met Asn Gln Ala Pro Thr Val Gly Phe Glu
 80 85 90
 Ala Asp Val Gly Gln Arg Ser Thr Leu Arg Val Val Ser His Thr Ser
 95 100 105 110
 Val Pro Leu Leu Leu Arg Asn Tyr Ser His Tyr Phe Gln Lys Ala Arg
 115 120 125
 Asp Thr Leu Tyr Met Val Trp Gly Gln Gly Arg His Met Asp Arg Val
 130 135 140
 Leu Gly Gly Arg Thr Tyr Arg Thr Leu Leu Gln Leu Thr Arg Met Tyr
 145 150 155
 Pro Gly Leu Gln Val Tyr Thr Phe Thr Glu Arg Met Met Ala Tyr Cys
 160 165 170
 Asp Gln Ile Phe Gln Asp Glu Thr Gly Lys Asn Arg Arg Gln Ser Gly
 175 180 185 190
 Ser Phe Leu Ser Thr Gly Trp Phe Thr Met Ile Leu Ala Leu Glu Leu
 195 200 205
 Cys Glu Glu Ile Val Val Tyr Gly Met Val Ser Asp Ser Tyr Cys Arg
 210 215 220
 Glu Lys Ser His Pro Ser Val Pro Tyr His Tyr Phe Glu Lys Gly Arg
 225 230 235
 Leu Asp Glu Cys Gln Met Tyr Leu Ala His Glu Gln Ala Pro Arg Ser
 240 245 250
 Ala His Arg Phe Ile Thr Glu Lys Ala Val Phe Ser Arg Trp Ala Lys
 255 260 265 270
 Lys Arg Pro Ile Val Phe Ala His Pro Ser Trp Arg Thr Glu
 275 280

<210> 76

<211> 249

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -15...-1

<400> 76

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Met Leu Gln Leu Trp Lys Leu Val Leu Leu Cys Gly Val Leu Thr Gly
-15                      -10                      -5                      1
Thr Ser Glu Ser Leu Leu Asp Asn Leu Gly Asn Asp Leu Ser Asn Val
      5                      10                      15
Val Asp Lys Leu Glu Pro Val Leu His Glu Gly Leu Glu Thr Val Asp
      20                      25                      30
Asn Thr Leu Lys Gly Ile Leu Glu Lys Leu Lys Val Asp Leu Gly Val
      35                      40                      45
Leu Gln Lys Ser Ser Ala Trp Gln Leu Ala Lys Gln Lys Ala Gln Glu
50                      55                      60                      65
Ala Glu Lys Leu Leu Asn Asn Val Ile Ser Lys Leu Leu Pro Thr Asn
      70                      75                      80
Thr Asp Ile Phe Gly Leu Lys Ile Ser Asn Ser Leu Ile Leu Asp Val
      85                      90                      95
Lys Ala Glu Pro Ile Asp Asp Gly Lys Gly Leu Asn Leu Ser Phe Pro
      100                      105                      110
Val Thr Ala Asn Val Thr Val Ala Gly Pro Ile Ile Gly Gln Ile Ile
      115                      120                      125
Asn Leu Lys Ala Ser Leu Asp Leu Leu Thr Ala Val Thr Ile Glu Thr
130                      135                      140                      145
Asp Pro Gln Thr His Gln Pro Val Ala Val Leu Gly Glu Cys Ala Ser
      150                      155                      160
Asp Pro Thr Ser Ile Ser Leu Ser Leu Leu Asp Lys His Ser Gln Ile
      165                      170                      175
Ile Asn Lys Phe Val Asn Ser Val Ile Asn Thr Leu Lys Ser Thr Val
      180                      185                      190
Ser Ser Leu Leu Gln Lys Glu Ile Cys Pro Leu Ile Arg Ile Phe Ile
      195                      200                      205
His Ser Leu Asp Val Asn Val Ile Gln Gln Val Val Asp Asn Pro Gln
210                      215                      220                      225
His Lys Thr Gln Leu Gln Thr Leu Ile
      230

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<210> 77

<211> 84

<212> PRT

<213> Homo Sapiens

<400> 77

129

Met Lys Val Lys Ile Lys Cys Trp Asn Gly Val Ala Thr Trp Leu Trp
 1 5 10 15
 Val Ala Asn Asp Glu Asn Cys Gly Ile Cys Arg Met Ala Phe Asn Gly
 20 25 30
 Cys Cys Pro Asp Cys Lys Val Pro Gly Asp Asp Cys Pro Leu Val Trp
 35 40 45
 Gly Gln Cys Ser His Cys Phe His Met His Cys Ile Leu Lys Trp Leu
 50 55 60
 His Ala Gln Gln Val Gln Gln His Cys Pro Met Cys Arg Gln Glu Trp
 65 70 75 80
 Lys Phe Lys Glu

<210> 78

<211> 554

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -13...-1

<220>

<221> UNSURE

<222> 259

<223> Xaa = Asp,His,Asn,Tyr

<400> 78

Met Leu Tyr Leu Gln Gly Trp Ser Met Pro Ala Val Ala Glu Val Lys
 -10 -5 1
 Leu Arg Asp Asp Gln Tyr Thr Leu Glu His Met His Ala Phe Gly Met
 5 10 15
 Tyr Asn Tyr Leu His Cys Asp Ser Trp Tyr Gln Asp Ser Val Tyr Tyr
 20 25 30 35
 Ile Asp Thr Leu Gly Arg Ile Met Asn Leu Thr Val Met Leu Asp Thr
 40 45 50
 Ala Leu Gly Lys Pro Arg Glu Val Phe Arg Leu Pro Thr Asp Leu Thr
 55 60 65
 Ala Cys Asp Asn Arg Leu Cys Ala Ser Ile His Phe Ser Ser Ser Thr
 70 75 80
 Trp Val Thr Leu Ser Asp Gly Thr Gly Arg Leu Tyr Val Ile Gly Thr
 85 90 95
 Gly Glu Arg Gly Asn Ser Ala Ser Glu Lys Trp Glu Ile Met Phe Asn

130

100	105	110	115
Glu Glu Leu Gly Asp Pro Phe Ile Ile Ile His Ser Ile Ser Leu Leu			
	120	125	130
Asn Ala Glu Glu His Ser Ile Ala Thr Leu Leu Leu Arg Ile Glu Lys			
	135	140	145
Glu Glu Leu Asp Met Lys Gly Ser Gly Phe Tyr Val Ser Leu Glu Trp			
	150	155	160
Val Thr Ile Ser Lys Lys Asn Gln Asp Asn Lys Lys Tyr Glu Ile Ile			
	165	170	175
Lys Arg Asp Ile Leu Arg Gly Lys Ser Val Pro His Tyr Ala Ala Ile			
180	185	190	195
Lys Pro Asp Gly Asn Gly Leu Met Ile Val Ser Tyr Lys Ser Leu Thr			
	200	205	210
Phe Val Gln Ala Gly Gln Asp Leu Glu Glu Asn Met Asp Glu Asp Ile			
	215	220	225
Ser Glu Lys Ile Lys Glu Pro Leu Tyr Tyr Trp Gln Gln Thr Glu Asp			
	230	235	240
Asp Leu Thr Val Thr Ile Arg Leu Pro Glu Asp Ser Thr Lys Glu Xaa			
	245	250	255
Ile Gln Ile Gln Phe Leu Pro Asp His Ile Asn Ile Val Leu Lys Asp			
260	265	270	275
His Gln Phe Leu Glu Gly Lys Leu Tyr Ser Ser Ile Asp His Glu Ser			
	280	285	290
Ser Thr Trp Ile Ile Lys Glu Ser Asn Ser Leu Glu Ile Ser Leu Ile			
	295	300	305
Lys Lys Asn Glu Gly Leu Thr Trp Pro Glu Leu Val Ile Gly Asp Lys			
	310	315	320
Gln Gly Glu Leu Ile Arg Asp Ser Ala Gln Cys Ala Ala Ile Ala Glu			
	325	330	335
Arg Leu Met His Leu Thr Ser Glu Glu Leu Asn Pro Asn Pro Asp Lys			
340	345	350	355
Glu Lys Pro Pro Cys Asn Ala Gln Glu Leu Glu Glu Cys Asp Ile Phe			
	360	365	370
Phe Glu Glu Ser Ser Ser Leu Cys Arg Phe Asp Gly Asn Thr Leu Lys			
	375	380	385
Thr Thr His Val Val Asn Leu Gly Ser Asn Gln Tyr Leu Phe Ser Val			
	390	395	400
Ile Val Asp Pro Lys Glu Met Pro Cys Phe Cys Leu Arg His Asp Val			
	405	410	415
Asp Ala Leu Leu Trp Gln Pro His Ser Ser Lys Gln Asp Asp Met Trp			
420	425	430	435
Glu His Ile Ala Thr Phe Asn Ala Leu Gly Tyr Val Gln Ala Ser Lys			

131

440 445 450
 Arg Asp Lys Lys Phe Phe Ala Cys Ala Pro Asn Tyr Ser Tyr Ala Ala
 455 460 465
 Leu Cys Glu Cys Leu Arg Arg Val Phe Ile Tyr Arg Gln Pro Ala Pro
 470 475 480
 Met Ser Thr Val Leu Tyr Asn Arg Lys Glu Gly Arg Gln Val Gly Gln
 485 490 495
 Val Ala Lys Gln Gln Val Ala Ser Leu Glu Thr Asn Asp Pro Ile Leu
 500 505 510 515
 Gly Phe Gln Ala Thr Asn Glu Arg Leu Phe Val Leu Thr Thr Lys Asn
 520 525 530
 Leu Phe Leu Ile Lys Val Asn Thr Glu Asn
 535 540

<210> 79

<211> 99

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -48...-1

<400> 79

Met Asp Asn Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser
 -45 -40 -35
 Val Lys Gly His Val Lys Met Leu Arg Leu Asp Ile Ile Asn Ser Leu
 -30 -25 -20
 Val Thr Thr Val Phe Met Leu Ile Val Ser Val Leu Ala Leu Ile Pro
 -15 -10 -5
 Glu Thr Thr Thr Leu Thr Val Gly Gly Gly Val Phe Ala Leu Val Thr
 1 5 10 15
 Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu
 20 25 30
 Phe Asn Pro Ser Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys
 35 40 45
 Glu Val Leu
 50

<210> 80

<211> 90

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -32...-1

<400> 80

```

Met Pro Cys Leu Asp Gln Gln Leu Thr Val His Ala Leu Pro Cys Pro
      -30                -25                -20
Ala Gln Pro Ser Ser Leu Ala Phe Cys Gln Val Gly Phe Leu Thr Ala
      -15                -10                -5
Gln Pro Ser Pro Pro Arg Arg Arg Asn Gly Lys Asp Arg Tyr Thr Leu
1              5              10              15
Val Leu Gln His Gln Glu Cys Gln Asp Asp Leu Ala Thr Ser Ser Leu
      20                25                30
Val Tyr Leu Ser Leu Pro Cys Phe Lys Asp Leu Gly Arg Ser Lys His
      35                40                45
Gln Ser Ile Thr Val Ala Asp Thr Asn Lys
      50                55

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<210> 81

<211> 115

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -46...-1

<400> 81

```

Met Lys Thr Leu Phe Asn Pro Ala Pro Ala Ile Ala Asp Leu Asp Pro
      -45                -40                -35
Gln Phe Tyr Thr Leu Ser Asp Val Phe Cys Cys Asn Glu Ser Glu Ala
      -30                -25                -20                -15
Glu Ile Leu Thr Gly Leu Thr Val Gly Ser Ala Ala Asp Ala Gly Glu
      -10                -5                1
Ala Ala Leu Val Leu Leu Lys Arg Gly Cys Gln Val Val Ile Ile Thr
      5              10              15
Leu Gly Ala Glu Gly Cys Val Val Leu Ser Gln Thr Glu Pro Glu Pro
      20                25                30
Lys His Ile Pro Thr Glu Lys Val Lys Ala Val Asp Thr Thr Cys Arg
      35                40                45                50

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Pro Gly Ser Arg Pro Lys Ser Glu Ala Ala Ser Val Lys Lys Gln Lys
55 60 65
His Tyr Lys

<210> 82
<211> 66
<212> PRT
<213> Homo Sapiens

<220>
<221> SIGNAL
<222> -19...-1

<400> 82
Met Lys Pro Leu Leu Val Val Phe Val Phe Leu Phe Leu Trp Asp Pro
-15 -10 -5
Val Leu Ala Gly Ile Asn Ser Leu Ser Ser Glu Met His Lys Lys Cys
1 5 10
Tyr Lys Asn Gly Ile Cys Arg Leu Glu Cys Tyr Glu Ser Glu Met Leu
15 20 25
Val Ala Tyr Cys Met Phe Gln Leu Glu Cys Cys Val Lys Gly Asn Pro
30 35 40 45
Ala Pro

<210> 83
<211> 133
<212> PRT
<213> Homo Sapiens

<220>
<221> SIGNAL
<222> -21...-1

<400> 83
Met Ser Cys Ser Leu Lys Phe Thr Leu Ile Val Ile Phe Phe Tyr Cys
-20 -15 -10
Trp Leu Ser Ser Ser His Glu Glu Leu Glu Gly Gly Thr Ser Lys Ser
-5 1 5 10
Phe Asp Leu His Thr Val Ile Met Leu Val Ile Ala Gly Gly Ile Leu
15 20 25
Ala Ala Leu Leu Leu Leu Ile Val Val Val Leu Cys Leu Tyr Phe Lys
30 35 40

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Ile His Asn Ala Leu Lys Ala Ala Lys Glu Pro Glu Ala Val Ala Val
 45 50 55
 Lys Asn His Asn Pro Asp Lys Val Trp Trp Ala Lys Asn Ser Gln Ala
 60 65 70 75
 Lys Thr Ile Ala Thr Glu Ser Cys Pro Ala Leu Gln Cys Cys Glu Gly
 80 85 90
 Tyr Arg Met Cys Ala Ser Phe Asp Ser Leu Pro Pro Cys Cys Cys Asp
 95 100 105
 Ile Asn Glu Gly Leu
 110

<210> 84

<211> 140

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -70..-1

<400> 84

Met Val Leu Thr Lys Pro Leu Gln Arg Asn Gly Ser Met Met Ser Phe
 -70 -65 -60 -55
 Glu Asn Val Lys Glu Lys Ser Arg Glu Gly Gly Pro His Ala His Thr
 -50 -45 -40
 Pro Glu Glu Glu Leu Cys Phe Val Val Thr His Tyr Pro Gln Val Gln
 -35 -30 -25
 Thr Thr Leu Asn Leu Phe Phe His Ile Phe Lys Val Leu Thr Gln Pro
 -20 -15 -10
 Leu Ser Leu Leu Trp Gly Cys Asp Gln Lys Pro Arg Thr Val Pro Thr
 -5 1 5 10
 Leu Gly Asn Gly Ala Trp Asp Thr Cys Gln Gln His Ile Arg Thr Ser
 15 20 25
 Ser Trp Thr Ala Asn Thr Leu Val Ile Gln Asn Gln His Ser Arg Glu
 30 35 40
 Ser Thr Val Ser Val Cys Leu Phe Met Leu Ile Arg Met Gln His Ile
 45 50 55
 Leu Lys Thr Asp Thr Leu Gln Gln Phe Arg Ile Cys
 60 65 70

<210> 85

<211> 233

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -32...-1

<400> 85

```

Met Ala Thr Pro Pro Phe Arg Leu Ile Arg Lys Met Phe Ser Phe Lys
      -30                -25                -20
Val Ser Arg Trp Met Gly Leu Ala Cys Phe Arg Ser Leu Ala Ala Ser
      -15                -10                -5
Ser Pro Ser Ile Arg Gln Lys Lys Leu Met His Lys Leu Gln Glu Glu
1           5           10           15
Lys Ala Phe Arg Glu Glu Met Lys Ile Phe Arg Glu Lys Ile Glu Asp
      20           25           30
Phe Arg Glu Glu Met Trp Thr Phe Arg Gly Lys Ile His Ala Phe Arg
      35           40           45
Gly Gln Ile Leu Gly Phe Trp Glu Glu Glu Arg Pro Phe Trp Glu Glu
      50           55           60
Glu Lys Thr Phe Trp Lys Glu Glu Lys Ser Phe Trp Glu Met Glu Lys
65           70           75           80
Ser Phe Arg Glu Glu Glu Lys Thr Phe Trp Lys Lys Tyr Arg Thr Phe
      85           90           95
Trp Lys Glu Asp Lys Ala Phe Trp Lys Glu Asp Asn Ala Leu Trp Glu
      100          105          110
Arg Asp Arg Asn Leu Leu Gln Glu Asp Lys Ala Leu Trp Glu Glu Glu
      115          120          125
Lys Ala Leu Trp Val Glu Glu Arg Ala Leu Leu Glu Gly Glu Lys Ala
      130          135          140
Leu Trp Glu Asp Lys Thr Ser Leu Trp Glu Glu Glu Asn Ala Leu Trp
145          150          155          160
Glu Glu Glu Arg Ala Phe Trp Met Glu Asn Asn Gly His Ile Ala Gly
      165          170          175
Glu Gln Met Leu Glu Asp Gly Pro His Asn Ala Asn Arg Gly Gln Arg
      180          185          190
Leu Leu Ala Phe Ser Arg Gly Arg Ala
      195          200

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<210> 86

<211> 83

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -29...-1

<400> 86

```

Met Ser Phe Phe Gln Leu Leu Met Lys Arg Lys Glu Leu Ile Pro Leu
      -25              -20              -15
Val Val Phe Met Thr Val Ala Ala Gly Gly Ala Ser Ser Phe Ala Val
      -10              -5              1
Tyr Ser Leu Trp Lys Thr Asp Val Ile Leu Asp Arg Lys Lys Asn Pro
      5              10              15
Glu Pro Trp Glu Thr Val Asp Pro Thr Val Pro Gln Lys Leu Ile Thr
20              25              30              35
Ile Asn Gln Gln Trp Lys Pro Ile Glu Glu Leu Gln Asn Val Gln Arg
      40              45              50
Val Thr Lys

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<210> 87

<211> 215

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -41...-1

<400> 87

```

Met Val Ser Ala Leu Arg Gly Ala Pro Leu Ile Arg Val His Ser Ser
      -40              -35              -30
Pro Val Ser Ser Pro Ser Val Ser Gly Pro Arg Arg Leu Val Ser Cys
      -25              -20              -15              -10
Leu Ser Ser Gln Ser Ser Ala Leu Ser Gln Ser Gly Gly Gly Ser Thr
      -5              1              5
Ser Ala Ala Gly Ile Glu Ala Arg Ser Arg Ala Leu Arg Arg Arg Trp
      10              15              20
Cys Pro Ala Gly Ile Met Leu Leu Ala Leu Val Cys Leu Leu Ser Cys
      25              30              35
Leu Leu Pro Ser Ser Glu Ala Lys Leu Tyr Gly Arg Cys Glu Leu Ala
      40              45              50              55
Arg Val Leu His Asp Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu

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137

60	65	70
Ala Asp Trp Val Cys Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala		
75	80	85
Ala Leu Asp Tyr Glu Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln		
90	95	100
Ile Asn Ser Arg Arg Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn		
105	110	115
Val Cys Arg Met Tyr Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp		
120	125	130
Thr Val Ile Cys Ala Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly		
140	145	150
Tyr Trp Glu Ala Trp Arg His His Cys Gln Gly Lys Asp Leu Thr Glu		
155	160	165
Trp Val Asp Gly Cys Asp Phe		
170		

<210> 88

<211> 417

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -20...-1

<400> 88

Met Met Gly Ser Pro Val Ser His Leu Leu Ala Gly Phe Cys Val Trp		
-20	-15	-10
Val Val Leu Gly Trp Val Gly Gly Ser Val Pro Asn Leu Gly Pro Ala		
1	5	10
Glu Gln Glu Gln Asn His Tyr Leu Ala Gln Leu Phe Gly Leu Tyr Gly		
15	20	25
Glu Asn Gly Thr Leu Thr Ala Gly Gly Leu Ala Arg Leu Leu His Ser		
30	35	40
Leu Gly Leu Gly Arg Val Gln Gly Leu Arg Leu Gly Gln His Gly Pro		
45	50	55
Leu Thr Gly Arg Ala Ala Ser Pro Ala Ala Asp Asn Ser Thr His Arg		
65	70	75
Pro Gln Asn Pro Glu Leu Ser Val Asp Val Trp Ala Gly Met Pro Leu		
80	85	90
Gly Pro Ser Gly Trp Gly Asp Leu Glu Glu Ser Lys Ala Pro His Leu		
95	100	105

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Pro Arg Gly Pro Ala Pro Ser Gly Leu Asp Leu Leu His Arg Leu Leu
 110 115 120
 Leu Leu Asp His Ser Leu Ala Asp His Leu Asn Glu Asp Cys Leu Asn
 125 130 135 140
 Gly Ser Gln Leu Leu Val Asn Phe Gly Leu Ser Pro Ala Ala Pro Leu
 145 150 155
 Thr Pro Arg Gln Phe Ala Leu Leu Cys Pro Ala Leu Leu Tyr Gln Ile
 160 165 170
 Asp Ser Arg Val Cys Ile Gly Ala Pro Ala Pro Ala Pro Pro Gly Asp
 175 180 185
 Leu Leu Ser Ala Leu Leu Gln Ser Ala Leu Ala Val Leu Leu Leu Ser
 190 195 200
 Leu Pro Ser Pro Leu Ser Leu Leu Leu Leu Arg Leu Leu Gly Pro Arg
 205 210 215 220
 Leu Leu Arg Pro Leu Leu Gly Phe Leu Gly Ala Leu Ala Val Gly Thr
 225 230 235
 Leu Cys Gly Asp Ala Leu Leu His Leu Leu Pro His Ala Gln Glu Gly
 240 245 250
 Arg His Ala Gly Pro Gly Gly Leu Pro Glu Lys Asp Leu Gly Pro Gly
 255 260 265
 Leu Ser Val Leu Gly Gly Leu Phe Leu Leu Phe Val Leu Glu Asn Met

Leu Gly Leu Leu Arg His Arg Gly Leu Arg Pro Arg Cys Cys Arg Arg
 285 290 295 300
 Lys Arg Arg Asn Leu Glu Thr Arg Asn Leu Asp Pro Glu Asn Gly Ser
 305 310 315
 Gly Met Ala Leu Gln Pro Leu Gln Ala Ala Pro Glu Pro Gly Ala Gln
 320 325 330
 Gly Gln Arg Glu Lys Asn Ser Gln His Pro Pro Ala Leu Ala Pro Pro
 335 340 345
 Gly His Gln Gly His Ser His Gly His Gln Gly Gly Thr Asp Ile Thr
 350 355 360
 Trp Met Val Leu Leu Gly Asp Gly Leu His Asn Leu Thr Asp Gly Leu
 365 370 375 380
 Ala Ile Gly Ala Ala Phe Ser Asp Gly Phe Ser Ala Ala Ser Val Pro
 385 390 395
 Pro

<210> 89

<211> 366

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -23...-1

<400> 89

Met Ala Ser Met Ala Ala Val Leu Thr Trp Ala Leu Ala Leu Leu Ser
-20 -15 -10
Ala Phe Ser Ala Thr Gln Ala Arg Lys Gly Phe Trp Asp Tyr Phe Ser
-5 1 5
Gln Thr Ser Gly Asp Lys Gly Arg Val Glu Gln Ile His Gln Gln Lys
10 15 20 25
Met Ala Arg Glu Pro Ala Thr Leu Lys Asp Ser Leu Glu Gln Asp Leu
30 35 40
Asn Asn Met Asn Lys Phe Leu Glu Lys Leu Arg Pro Leu Ser Gly Ser
45 50 55
Glu Ala Pro Arg Leu Pro Gln Asp Pro Val Gly Met Arg Arg Gln Leu
60 65 70
Gln Glu Glu Leu Glu Glu Val Lys Ala Arg Leu Gln Pro Tyr Met Ala
75 80 85
Glu Ala His Glu Leu Val Gly Trp Asn Leu Glu Gly Leu Arg Gln Gln
90 95 100 105
Leu Lys Pro Tyr Thr Met Asp Leu Met Glu Gln Val Ala Leu Arg Val
110 115 120
Gln Glu Leu Gln Glu Gln Leu Arg Val Val Gly Glu Asp Thr Lys Ala
125 130 135
Gln Leu Leu Gly Gly Val Asp Glu Ala Trp Ala Leu Leu Gln Gly Leu
140 145 150
Gln Ser Arg Val Val His His Thr Gly Arg Phe Lys Glu Leu Phe His
155 160 165
Pro Tyr Ala Glu Ser Leu Val Ser Gly Ile Gly Arg His Val Gln Glu
170 175 180 185
Leu His Arg Ser Val Ala Pro His Ala Pro Ala Ser Pro Ala Arg Leu
190 195 200
Ser Arg Cys Val Gln Val Leu Ser Arg Lys Leu Thr Leu Lys Ala Lys
205 210 215
Ala Leu His Ala Arg Ile Gln Gln Asn Leu Asp Gln Leu Arg Glu Glu
220 225 230
Leu Ser Arg Ala Phe Ala Gly Thr Gly Thr Glu Glu Gly Ala Gly Pro
235 240 245
Asp Pro Gln Met Leu Ser Glu Glu Val Arg Gln Arg Leu Gln Ala Phe
250 255 260 265

140

Arg Gln Asp Thr Tyr Leu Gln Ile Ala Ala Phe Thr Arg Ala Ile Asp
 270 275 280
 Gln Glu Thr Glu Glu Val Gln Gln Gln Leu Ala Pro Pro Pro Pro Gly
 285 290 295
 His Ser Ala Phe Ala Pro Glu Phe Gln Gln Thr Asp Ser Gly Lys Val
 300 305 310
 Leu Ser Lys Leu Gln Ala Arg Leu Asp Asp Leu Trp Glu Asp Ile Thr
 315 320 325
 His Ser Leu His Asp Gln Gly His Ser His Leu Gly Asp Pro
 330 335 340

<210> 90

<211> 150

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -45...-1

<400> 90

Met Val Leu Met Trp Thr Ser Gly Asp Ala Phe Lys Thr Ala Tyr Phe
 -45 -40 -35 -30
 Leu Leu Lys Gly Ala Pro Leu Gln Phe Ser Val Cys Gly Leu Leu Gln
 -25 -20 -15
 Val Leu Val Asp Leu Ala Ile Leu Gly Gln Ala Tyr Ala Phe Ala Pro
 -10 -5 1
 Pro Pro Glu Ala Gly Ala Pro Arg Arg Ala Pro His Trp His Gln Gly
 5 10 15
 Pro Leu Thr Val Gly Arg Thr Arg Met Trp Asp Arg Gln Pro Arg Ala
 20 25 30 35
 Leu Val Gly Pro Asp Leu Pro Ala Gly Arg Val Gly Ala Val Ala Pro
 40 45 50
 Ala Gly Val Ala Glu Met Gly His Gly His Trp Gly Leu His Gln Pro
 55 60 65
 Leu Trp Gly Val Ser Gly Trp Ala Val Gly Val Gly Leu Gly Arg Cys
 70 75 80
 Leu Cys Ser Ala Gly Thr Ala Arg Val Asp Leu Ala Pro Arg Val Leu
 85 90 95
 Asp Val Phe Arg Met Thr
 100 105

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<220>
<221> SIGNAL
<222> -68..-1
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<400> 91
Met Asp Phe Val Ala Gly Ala Ile Gly Gly Val Cys Gly Val Ala Val
      -65                      -60                      -55
Gly Tyr Pro Leu Asp Thr Val Lys Val Arg Ile Gln Thr Glu Pro Lys
      -50                      -45                      -40
Tyr Thr Gly Ile Trp His Cys Val Arg Asp Thr Tyr His Arg Glu Arg
      -35                      -30                      -25
Val Trp Gly Phe Tyr Arg Gly Leu Ser Leu Pro Val Cys Thr Val Ser
      -20                      -15                      -10                      -5
Leu Val Ser Ser Val Ser Phe Gly Thr Tyr Arg His Cys Leu Ala His
      1                      5                      10
Ile Cys Arg Leu Arg Tyr Gly Asn Pro Asp Ala Lys Pro Thr Lys Ala
      15                      20                      25
Asp Ile Thr Leu Ser Gly Cys Ala Ser Gly Leu Val Arg Val Phe Leu
      30                      35                      40
Thr Ser Pro Thr Glu Val Ala Lys Val Arg Leu Gln Thr Gln Thr Gln
      45                      50                      55                      60
Ala Gln Lys Gln Gln Arg Leu Leu Ser Ala Ser Gly Pro Leu Ala Val
      65                      70                      75
Pro Pro Met Cys Pro Val Pro Pro Ala Cys Pro Glu Pro Lys Tyr Arg
      80                      85                      90
Gly Pro Leu His Cys Leu Ala Thr Val Ala Arg Glu Glu Gly Leu Cys
      95                      100                      105
Gly Leu Tyr Lys Gly Ser Ser Ala Leu Val Leu Arg Asp Gly His Ser
      110                      115                      120
Phe Ala Thr Tyr Phe Leu Ser Tyr Ala Val Leu Cys Glu Trp Leu Ser
      125                      130                      135                      140
Pro Ala Gly His Ser Arg Pro Asp Val Pro Gly Val Leu Val Ala Gly
      145                      150                      155
Gly Cys Ala Gly Val Leu Ala Trp Ala Val Ala Thr Pro Met Asp Val
      160                      165                      170
Ile Lys Ser Arg Leu Gln Ala Asp Gly Gln Gly Gln Arg Arg Tyr Arg
      175                      180                      185

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Gly Leu Leu His Cys Met Val Thr Ser Val Arg Glu Glu Gly Pro Arg
 190 195 200
 Val Leu Phe Lys Gly Leu Val Leu Asn Cys Cys Arg Ala Phe Pro Val
 205 210 215 220
 Asn Met Val Val Phe Val Ala Tyr Glu Ala Val Leu Arg Leu Ala Arg
 225 230 235
 Gly Leu Leu Thr
 240

<210> 92

<211> 114

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -49...-1

<400> 92

Met Glu Lys Pro Leu Phe Pro Leu Val Pro Leu His Trp Phe Gly Phe
 -45 -40 -35
 Gly Tyr Thr Ala Leu Val Val Ser Gly Gly Ile Val Gly Tyr Val Lys
 -30 -25 -20
 Thr Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu
 -15 -10 -5
 Ala Gly Leu Gly Ala Tyr Gln Leu Tyr Gln Asp Pro Arg Asn Val Trp
 1 5 10 15
 Gly Phe Leu Ala Ala Thr Ser Val Thr Phe Val Gly Val Met Gly Met
 20 25 30
 Arg Ser Tyr Tyr Tyr Gly Lys Phe Met Pro Val Gly Leu Ile Ala Gly
 35 40 45
 Ala Ser Leu Leu Met Ala Ala Lys Val Gly Val Arg Met Leu Met Thr
 50 55 60
 Ser Asp
 65

<210> 93

<211> 382

<212> PRT

<213> Homo Sapiens

<220>

<222> -15..-1

Met	Gly	Leu	Leu	Leu	Pro	Pro	Leu	Ala	Leu	Cys	Ile	Leu	Val	Leu	Cys	Cys
-15					-10						-5					1
Gly	Ala	Met	Ser	Pro	Pro	Gln	Leu	Ala	Leu	Asn	Pro	Ser	Ala	Leu	Leu	
		5						10					15			
Ser	Arg	Gly	Cys	Asn	Asp	Ser	Asp	Val	Leu	Ala	Val	Ala	Gly	Phe	Ala	
	20						25					30				
Leu	Arg	Asp	Ile	Asn	Lys	Asp	Arg	Lys	Asp	Gly	Tyr	Val	Leu	Arg	Leu	
	35					40					45					
Asn	Arg	Val	Asn	Asp	Ala	Gln	Glu	Tyr	Arg	Arg	Gly	Gly	Leu	Gly	Ser	
50					55					60					65	
Leu	Phe	Tyr	Leu	Thr	Leu	Asp	Val	Leu	Glu	Thr	Asp	Cys	His	Val	Leu	
			70						75					80		
Arg	Lys	Lys	Ala	Trp	Gln	Asp	Cys	Gly	Met	Arg	Ile	Phe	Phe	Glu	Ser	
		85						90					95			
Val	Tyr	Gly	Gln	Cys	Lys	Ala	Ile	Phe	Tyr	Met	Asn	Asn	Pro	Ser	Arg	
	100						105					110				
Val	Leu	Tyr	Leu	Ala	Ala	Tyr	Asn	Cys	Thr	Leu	Arg	Pro	Val	Ser	Lys	
	115					120					125					
Lys	Lys	Ile	Tyr	Met	Thr	Cys	Pro	Asp	Cys	Pro	Ser	Ser	Ile	Pro	Thr	
130					135					140					145	
Asp	Ser	Ser	Asn	His	Gln	Val	Leu	Glu	Ala	Ala	Thr	Glu	Ser	Leu	Ala	
			150						155					160		
Lys	Tyr	Asn	Asn	Glu	Asn	Thr	Ser	Lys	Gln	Tyr	Ser	Leu	Phe	Lys	Val	
		165						170					175			
Thr	Arg	Ala	Ser	Ser	Gln	Trp	Val	Val	Gly	Pro	Ser	Tyr	Phe	Val	Glu	
	180						185					190				
Tyr	Leu	Ile	Lys	Glu	Ser	Pro	Cys	Thr	Lys	Ser	Gln	Ala	Ser	Ser	Cys	
	195					200					205					
Ser	Leu	Gln	Ser	Ser	Asp	Ser	Val	Pro	Val	Gly	Leu	Cys	Lys	Gly	Ser	
210					215					220					225	
Leu	Thr	Arg	Thr	His	Trp	Glu	Lys	Phe	Val	Ser	Val	Thr	Cys	Asp	Phe	
		230							235					240		
Phe	Glu	Ser	Gln	Ala	Pro	Ala	Thr	Gly	Ser	Glu	Asn	Ser	Ala	Val	Asn	
	245							250					255			
Gln	Lys	Pro	Thr	Asn	Leu	Pro	Lys	Val	Glu	Glu	Ser	Gln	Gln	Lys	Asn	
	260						265					270				
Thr	Pro	Pro	Thr	Asp	Ser	Pro	Ser	Lys	Ala	Gly	Pro	Arg	Gly	Ser	Val	
	275					280					285					

144

Gln Tyr Leu Pro Asp Leu Asp Asp Lys Asn Ser Gln Glu Lys Gly Pro
 290 295 300 305
 Gln Glu Ala Phe Pro Val His Leu Asp Leu Thr Thr Asn Pro Gln Gly
 310 315 320
 Glu Thr Leu Asp Ile Ser Phe Leu Phe Leu Glu Pro Met Glu Glu Lys
 325 330 335
 Leu Val Val Leu Pro Phe Pro Lys Glu Lys Ala Arg Thr Ala Glu Cys
 340 345 350
 Pro Gly Pro Ala Gln Asn Ala Ser Pro Leu Val Leu Pro Pro
 355 360 365

<210> 94

<211> 212

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -197...-1

<220>

<221> UNSURE

<222> -88

<223> Xaa = Ala, Asp, Gly, Val

<220>

<221> UNSURE

<222> -109

<223> Xaa = Asp, Glu

<400> 94

Met Ala Thr Pro Asn Asn Leu Thr Pro Thr Asn Cys Ser Trp Trp Pro
 -195 -190 -185
 Ile Ser Ala Leu Glu Ser Asp Ala Ala Lys Pro Ala Glu Ala Pro Asp
 -180 -175 -170
 Ala Pro Glu Ala Ala Ser Pro Ala His Trp Pro Arg Glu Ser Leu Val
 -165 -160 -155 -150
 Leu Tyr His Trp Thr Gln Ser Phe Ser Ser Gln Lys Ala Lys Ile Leu
 -145 -140 -135
 Glu His Asp Asp Val Ser Tyr Leu Lys Lys Ile Leu Gly Glu Leu Ala
 -130 -125 -120
 Met Val Leu Asp Gln Ile Glu Ala Xaa Leu Glu Lys Arg Lys Leu Glu

145

-115 -110 -105
 Asn Glu Gly Gln Lys Cys Glu Leu Trp Leu Cys Gly Cys Xaa Phe Thr
 -100 -95 -90
 Leu Ala Asp Val Leu Leu Gly Ala Thr Leu His Arg Leu Lys Phe Leu
 -85 -80 -75 -70
 Gly Leu Ser Lys Lys Tyr Trp Glu Asp Gly Ser Arg Pro Asn Leu Gln
 -65 -60 -55
 Ser Phe Phe Glu Arg Val Gln Arg Arg Phe Ala Phe Arg Lys Val Leu
 -50 -45 -40
 Gly Asp Ile His Thr Thr Leu Leu Ser Ala Val Ile Pro Asn Ala Phe
 -35 -30 -25
 Arg Leu Val Lys Arg Lys Pro Pro Ser Phe Phe Gly Ala Ser Phe Leu
 -20 -15 -10
 Met Gly Ser Leu Gly Gly Met Gly Tyr Phe Ala Tyr Trp Tyr Leu Lys
 -5 1 5 10
 Lys Lys Tyr Ile
 15

<210> 95

<211> 287

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -26...-1

<400> 95

Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly
 -25 -20 -15
 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg
 -10 -5 1 5
 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu
 10 15 20
 Leu Arg Leu Leu Asp Lys Thr Leu Ser Ala Arg Ser Pro Gly Lys His
 25 30 35
 Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg Pro Tyr
 40 45 50
 Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu Val Ile
 55 60 65 70
 Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly Gly Lys
 75 80 85

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Met Ser Gln Tyr Leu Asp Ser Leu Lys Val Gly Asp Val Val Glu Phe
 90 95 100
 Arg Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His Phe Asn
 105 110 115
 Ile Gln Pro Asn Lys Lys Ser Pro Pro Glu Pro Arg Val Ala Lys Lys
 120 125 130
 Leu Gly Met Ile Ala Gly Gly Thr Gly Ile Thr Pro Met Leu Gln Leu
 135 140 145 150
 Ile Arg Ala Ile Leu Lys Val Pro Glu Asp Pro Thr Gln Cys Phe Leu
 155 160 165
 Leu Phe Ala Asn Gln Thr Glu Lys Asp Ile Ile Leu Arg Glu Asp Leu
 170 175 180
 Glu Glu Leu Gln Ala Arg Tyr Pro Asn Arg Phe Lys Leu Trp Phe Thr
 185 190 195
 Leu Asp His Pro Pro Lys Asp Trp Ala Tyr Ser Lys Gly Phe Val Thr
 200 205 210
 Ala Asp Met Ile Arg Glu His Leu Pro Ala Pro Gly Asp Asp Val Leu
 215 220 225 230
 Val Leu Leu Cys Gly Pro Pro Pro Met Val Gln Leu Ala Cys His Pro
 235 240 245
 Asn Leu Asp Lys Leu Gly Tyr Ser Gln Lys Met Arg Phe Thr Tyr
 250 255 260

<210> 96

<211> 312

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -25...-1

<400> 96

Met Ser Asp Leu Leu Leu Leu Gly Leu Ile Gly Gly Leu Thr Leu Leu
 -25 -20 -15 -10
 Leu Leu Leu Thr Leu Leu Ala Phe Ala Gly Tyr Ser Gly Leu Leu Ala
 -5 1 5
 Gly Val Glu Val Ser Ala Gly Ser Pro Pro Ile Arg Asn Val Thr Val
 10 15 20
 Ala Tyr Lys Phe His Met Gly Leu Tyr Gly Glu Thr Gly Arg Leu Phe
 25 30 35
 Thr Glu Ser Cys Ile Ser Pro Lys Leu Arg Ser Ile Ala Val Tyr Tyr

147

40 45 50 55
 Asp Asn Pro His Met Val Pro Pro Asp Lys Cys Arg Cys Ala Val Gly
 60 65 70
 Ser Ile Leu Ser Glu Gly Glu Glu Ser Pro Ser Pro Glu Leu Ile Asp
 75 80 85
 Leu Tyr Gln Lys Phe Gly Phe Lys Val Phe Ser Phe Pro Ala Pro Ser
 90 95 100
 His Val Val Thr Ala Thr Phe Pro Tyr Thr Thr Ile Leu Ser Ile Trp
 105 110 115
 Leu Ala Thr Arg Arg Val His Pro Ala Leu Asp Thr Tyr Ile Lys Glu
 120 125 130 135
 Arg Lys Leu Cys Ala Tyr Pro Arg Leu Glu Ile Tyr Gln Glu Asp Gln
 140 145 150
 Ile His Phe Met Cys Pro Leu Ala Arg Gln Gly Asp Phe Tyr Val Pro
 155 160 165
 Glu Met Lys Glu Thr Glu Trp Lys Trp Arg Gly Leu Val Glu Ala Ile
 170 175 180
 Asp Thr Gln Val Asp Gly Thr Gly Ala Asp Thr Met Ser Asp Thr Ser
 185 190 195
 Ser Val Ser Leu Glu Val Ser Pro Gly Ser Arg Glu Thr Ser Ala Ala
 200 205 210 215
 Thr Leu Ser Pro Gly Ala Ser Ser Arg Gly Trp Asp Asp Gly Asp Thr
 220 225 230
 Arg Ser Glu His Ser Tyr Ser Glu Ser Gly Ala Ser Gly Ser Ser Phe
 235 240 245
 Glu Glu Leu Asp Leu Glu Gly Glu Gly Pro Leu Gly Glu Ser Arg Leu
 250 255 260
 Asp Pro Gly Thr Glu Pro Leu Gly Thr Thr Lys Trp Leu Trp Glu Pro
 265 270 275
 Thr Ala Pro Glu Lys Gly Lys Glu
 280 285

<210> 97

<211> 226

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -29...-1

<400> 97

148

Met Glu Thr Val Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe
 -25 -20 -15
 Leu Ala Ser Phe Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys
 -10 -5 1
 Arg Pro Arg Asp Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp
 5 10 15
 Leu Ile Gly Ala Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu
 20 25 30 35
 Asp Asp Val Val Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn
 40 45 50
 Glu Asp Trp Ile Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala
 55 60 65
 Ile Leu Lys Ile Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr
 70 75 80
 Met Gly Ser Gly Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile
 85 90 95
 Ile Val Val Ala Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys
 100 105 110 115
 Ser Met Tyr Pro Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr
 120 125 130
 Ala Leu Leu Leu Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala
 135 140 145
 Cys His Leu Thr Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala
 150 155 160
 Ala Glu Glu His Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu
 165 170 175
 Pro Asp Lys Gly Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser
 180 185 190 195
 Ala Ile

<210> 98

<211> 406

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -35...-1

<400> 98

Met Arg Gly Ser Val Glu Cys Thr Trp Gly Trp Gly His Cys Ala Pro
 -35 -30 -25 -20

149

Ser Pro Leu Leu Leu Trp Thr Leu Leu Leu Phe Ala Ala Pro Phe Gly
 -15 -10 -5
 Leu Leu Gly Glu Lys Thr Arg Gln Val Ser Leu Glu Val Ile Pro Asn
 1 5 10
 Trp Leu Gly Pro Leu Gln Asn Leu Leu His Ile Arg Ala Val Gly Thr
 15 20 25
 Asn Ser Thr Leu His Tyr Val Trp Ser Ser Leu Gly Pro Leu Ala Val
 30 35 40 45
 Val Met Val Ala Thr Asn Thr Pro His Ser Thr Leu Ser Val Asn Trp
 50 55 60
 Ser Leu Leu Leu Ser Pro Glu Pro Asp Gly Gly Leu Met Val Leu Pro
 65 70 75
 Lys Asp Ser Ile Gln Phe Ser Ser Ala Leu Val Phe Thr Arg Leu Leu
 80 85 90
 Glu Phe Asp Ser Thr Asn Val Ser Asp Thr Ala Ala Lys Pro Leu Gly
 95 100 105
 Arg Pro Tyr Pro Pro Tyr Ser Leu Ala Asp Phe Ser Trp Asn Asn Ile
 110 115 120 125
 Thr Asp Ser Leu Asp Pro Ala Thr Leu Ser Ala Thr Phe Gln Gly His
 130 135 140
 Pro Met Asn Asp Pro Thr Arg Thr Phe Ala Asn Gly Ser Leu Ala Phe
 145 150 155
 Arg Val Gln Ala Phe Ser Arg Ser Ser Arg Pro Ala Gln Pro Pro Arg
 160 165 170
 Leu Leu His Thr Ala Asp Thr Cys Gln Leu Glu Val Ala Leu Ile Gly
 175 180 185
 Ala Ser Pro Arg Gly Asn Arg Ser Leu Phe Gly Leu Glu Val Ala Thr
 190 195 200 205
 Leu Gly Gln Gly Pro Asp Cys Pro Ser Met Gln Glu Gln His Ser Ile
 210 215 220
 Asp Asp Glu Tyr Ala Pro Ala Val Phe Gln Leu Asp Gln Leu Trp
 225 230 235
 Gly Ser Leu Pro Ser Gly Phe Ala Gln Trp Arg Pro Val Ala Tyr Ser
 240 245 250
 Gln Lys Pro Gly Gly Arg Glu Ser Ala Leu Pro Cys Gln Ala Ser Pro
 255 260 265
 Leu His Pro Ala Leu Ala Tyr Ser Leu Pro Gln Ser Pro Ile Val Arg
 270 275 280 285
 Ala Phe Phe Gly Ser Gln Asn Asn Phe Cys Ala Phe Asn Leu Thr Phe
 290 295 300
 Gly Ala Ser Thr Gly Pro Gly Tyr Trp Asp Gln His Tyr Leu Ser Trp
 305 310 315

150

Ser Met Leu Leu Gly Val Gly Phe Pro Pro Val Asp Gly Leu Ser Pro
 320 325 330
 Leu Val Leu Gly Ile Met Ala Val Ala Leu Gly Ala Pro Gly Leu Met
 335 340 345
 Leu Leu Gly Gly Gly Leu Val Leu Leu Leu His His Lys Lys Tyr Ser
 350 355 360 365
 Glu Tyr Gln Ser Ile Asn
 370

<210> 99

<211> 120

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -57...-1

<400> 99

Met Met Pro Ser Arg Thr Asn Leu Ala Thr Gly Ile Pro Ser Ser Lys
 -55 -50 -45
 Val Lys Tyr Ser Arg Leu Ser Ser Thr Asp Asp Gly Tyr Ile Asp Leu
 -40 -35 -30
 Gln Phe Lys Lys Thr Pro Pro Lys Ile Pro Tyr Lys Ala Ile Ala Leu
 -25 -20 -15 -10
 Ala Thr Val Leu Phe Leu Ile Gly Ala Phe Leu Ile Ile Ile Gly Ser
 -5 1 5
 Leu Leu Leu Ser Gly Tyr Ile Ser Lys Gly Gly Ala Asp Arg Ala Val
 10 15 20
 Pro Val Leu Ile Ile Gly Ile Leu Val Phe Leu Pro Gly Phe Tyr His
 25 30 35
 Leu Arg Ile Ala Tyr Tyr Ala Ser Lys Gly Tyr Arg Gly Tyr Ser Tyr
 40 45 50 55
 Asp Asp Ile Pro Asp Phe Asp Asp
 60

<210> 100

<211> 210

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -36...-1

<400> 100

```

Met Ala Leu Pro Gln Met Cys Asp Gly Ser His Leu Ala Ser Thr Leu
  -35                -30                -25
Arg Tyr Cys Met Thr Val Ser Gly Thr Val Val Leu Val Ala Gly Thr
-20                -15                -10                -5
Leu Cys Phe Ala Trp Trp Ser Glu Gly Asp Ala Thr Ala Gln Pro Gly
          1                5                10
Gln Leu Ala Pro Pro Thr Glu Tyr Pro Val Pro Glu Gly Pro Ser Pro
      15                20                25
Leu Leu Arg Ser Val Ser Phe Val Cys Cys Gly Ala Gly Gly Leu Leu
      30                35                40
Leu Leu Ile Gly Leu Leu Trp Ser Val Lys Ala Ser Ile Pro Gly Pro
45                50                55                60
Pro Arg Trp Asp Pro Tyr His Leu Ser Arg Asp Leu Tyr Tyr Leu Thr
          65                70                75
Val Glu Ser Ser Glu Lys Glu Ser Cys Arg Thr Pro Lys Val Val Asp
          80                85                90
Ile Pro Thr Tyr Glu Glu Ala Val Ser Phe Pro Val Ala Glu Gly Pro
      95                100                105
Pro Thr Pro Pro Ala Tyr Pro Thr Glu Glu Ala Leu Glu Pro Ser Gly
      110                115                120
Ser Arg Asp Ala Leu Leu Ser Thr Gln Pro Ala Trp Pro Pro Pro Ser
125                130                135                140
Tyr Glu Ser Ile Ser Leu Ala Leu Asp Ala Val Ser Ala Glu Thr Thr
          145                150                155
Pro Ser Ala Thr Arg Ser Cys Ser Gly Leu Val Gln Thr Ala Arg Gly
          160                165                170
Gly Ser

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<210> 101

<211> 251

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -243...-1

<400> 101

```

Met Ala His Arg Leu Gln Ile Arg Leu Leu Thr Trp Asp Val Lys Asp
      -240              -235              -230
Thr Leu Leu Arg Leu Arg His Pro Leu Gly Glu Ala Tyr Ala Thr Lys
      -225              -220              -215
Ala Arg Ala His Gly Leu Glu Val Glu Pro Ser Ala Leu Glu Gln Gly
      -210              -205              -200
Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe Pro Asn Tyr Gly
      -195              -190              -185              -180
Leu Ser His Gly Leu Thr Ser Arg Gln Trp Trp Leu Asp Val Val Leu
      -175              -170              -165
Gln Thr Phe His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro
      -160              -155              -150
Ile Ala Glu Gln Leu Tyr Lys Asp Phe Ser His Pro Cys Thr Trp Gln
      -145              -140              -135
Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly
      -130              -125              -120
Leu Arg Leu Ala Val Ile Ser Asn Phe Asp Arg Arg Leu Glu Gly Ile
      -115              -110              -105              -100
Leu Glu Gly Leu Gly Leu Arg Glu His Phe Asp Phe Val Leu Thr Ser
      -95              -90              -85
Glu Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala
      -80              -75              -70
Leu Arg Leu Ala His Met Glu Pro Val Val Ala Ala His Val Gly Asp
      -65              -60              -55
Asn Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala Val Gly Met His Ser
      -50              -45              -40
Phe Leu Val Val Gly Pro Gln Ala Leu Asp Pro Val Val Arg Asp Ser
      -35              -30              -25              -20
Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala His Leu Leu Pro Ala
      -15              -10              -5
Leu Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu

```

1

5

<210> 102

<211> 126

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -24...-1

<400> 102

```

Met Asp Lys Ser Leu Leu Leu Glu Leu Pro Ile Leu Leu Cys Cys Phe
          -20                      -15                      -10
Arg Ala Leu Ser Gly Ser Leu Ser Met Arg Asn Asp Ala Val Asn Glu
          -5                      1                      5
Ile Val Ala Val Lys Asn Asn Phe Pro Val Ile Glu Ile Ile Gln Cys
    10                      15                      20
Arg Met Cys His Leu Gln Phe Pro Gly Glu Lys Cys Ser Arg Gly Arg
25                      30                      35                      40
Gly Ile Cys Thr Ala Thr Thr Glu Glu Ala Cys Met Val Gly Arg Met
          45                      50                      55
Phe Lys Arg Asp Gly Asn Pro Trp Leu Thr Phe Met Gly Cys Leu Lys
          60                      65                      70
Asn Cys Ala Asp Val Lys Gly Ile Arg Trp Ser Val Tyr Leu Val Asn
          75                      80                      85
Phe Arg Cys Cys Arg Ser His Asp Leu Cys Asn Glu Asp Leu
    90                      95                      100

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<210> 103

<211> 133

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -44...-1

<400> 103

```

Met Asp Arg Arg Ala Thr Ser Phe Pro Pro Leu Pro Ala Lys Glu Arg
          -40                      -35                      -30
Arg Ala Gly Ile Ser Ser Ala Leu Pro Cys Pro Pro Thr Met Ser Leu
          -25                      -20                      -15
Ser Asp Ser Leu Trp Ser Pro His Cys Ser Trp Ser Glu Arg Pro His
          -10                      -5                      1
Ser Phe Ser His Trp Arg Gln Pro Arg Met Gly Ser Ser Gly Gly Ser
5                      10                      15                      20
Leu Asp Tyr Val Ser Phe Lys His Trp Ile His Ser Ser Arg Ser Lys
          25                      30                      35
Gly Lys Ile Ala Ala Leu Glu Ala Gly Leu Phe Ile Ser Cys Leu Gly
          40                      45                      50
Asp Ala Pro Arg Gly Leu Asn Ala Ser Gln Gly Asn Gln Arg Lys Asn
    55                      60                      65

```

154

Met Val Cys Phe Arg Gly Gly Val Ala Ser Leu Ala Leu Pro Ser Leu
 70 75 80

Thr Pro Ser Cys Leu
 85

<210> 104

<211> 221

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -28...-1

<400> 104

Met Glu Ala Gly Gly Phe Leu Asp Ser Leu Ile Tyr Gly Ala Cys Val
 -25 -20 -15

Val Phe Thr Leu Gly Met Phe Ser Ala Gly Leu Ser Asp Leu Arg His
 -10 -5 1

Met Arg Met Thr Arg Ser Val Asp Asn Val Gln Phe Leu Pro Phe Leu
 5 10 15 20

Thr Thr Glu Val Asn Asn Leu Gly Trp Leu Ser Tyr Gly Ala Leu Lys
 25 30 35

Gly Asp Gly Ile Leu Ile Val Val Asn Thr Val Gly Ala Ala Leu Gln
 40 45 50

Thr Leu Tyr Ile Leu Ala Tyr Leu His Tyr Cys Pro Arg Lys Arg Val
 55 60 65

Val Leu Leu Gln Thr Ala Thr Leu Leu Gly Val Leu Leu Leu Gly Tyr
 70 75 80

Gly Tyr Phe Trp Leu Leu Val Pro Asn Pro Glu Ala Arg Leu Gln Gln
 85 90 95 100

Leu Gly Leu Phe Cys Ser Val Phe Thr Ile Ser Met Tyr Leu Ser Pro
 105 110 115

Leu Ala Asp Leu Ala Lys Val Ile Gln Thr Lys Ser Thr Gln Cys Leu
 120 125 130

Ser Tyr Pro Leu Thr Ile Ala Thr Leu Leu Thr Ser Ala Ser Trp Cys
 135 140 145

Leu Tyr Gly Phe Arg Leu Arg Asp Pro Tyr Ile Met Val Ser Asn Phe
 150 155 160

Pro Gly Ile Val Thr Ser Phe Ile Arg Phe Trp Leu Phe Trp Lys Tyr
 165 170 175 180

Pro Gln Glu Gln Asp Arg Asn Tyr Trp Leu Leu Gln Thr

155

185

190

<210> 105

<211> 352

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -23...-1

<400> 105

```

Met Glu Ser Gly Gly Arg Pro Ser Leu Cys Gln Phe Ile Leu Leu Gly
      -20              -15              -10
Thr Thr Ser Val Val Thr Ala Ala Leu Tyr Ser Val Tyr Arg Gln Lys
      -5              1              5
Ala Arg Val Ser Gln Glu Leu Lys Gly Ala Lys Lys Val His Leu Gly
10              15              20              25
Glu Asp Leu Lys Ser Ile Leu Ser Glu Ala Pro Gly Lys Cys Val Pro
      30              35              40
Tyr Ala Val Ile Glu Gly Ala Val Arg Ser Val Lys Glu Thr Leu Asn
      45              50              55
Ser Gln Phe Val Glu Asn Cys Lys Gly Val Ile Gln Arg Leu Thr Leu
      60              65              70
Gln Glu His Lys Met Val Trp Asn Arg Thr Thr His Leu Trp Asn Asp
      75              80              85
Cys Ser Lys Ile Ile His Gln Arg Thr Asn Thr Val Pro Phe Asp Leu
90              95              100              105
Val Pro His Glu Asp Gly Val Asp Val Ala Val Arg Val Leu Lys Pro
      110              115              120
Leu Asp Ser Val Asp Leu Gly Leu Glu Thr Val Tyr Glu Lys Phe His
      125              130              135
Pro Ser Ile Gln Ser Phe Thr Asp Val Ile Gly His Tyr Ile Ser Gly
      140              145              150
Glu Arg Pro Lys Gly Ile Gln Glu Thr Glu Glu Met Leu Lys Val Gly
      155              160              165
Ala Thr Leu Thr Gly Val Gly Glu Leu Val Leu Asp Asn Asn Ser Val
170              175              180              185
Arg Leu Gln Pro Pro Lys Gln Gly Met Gln Tyr Tyr Leu Ser Ser Gln
      190              195              200
Asp Phe Asp Ser Leu Leu Gln Arg Gln Glu Ser Ser Val Arg Leu Trp
      205              210              215

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156

Lys Val Leu Ala Leu Val Phe Gly Phe Ala Thr Cys Ala Thr Leu Phe
 220 225 230
 Phe Ile Leu Arg Lys Gln Tyr Leu Gln Arg Gln Glu Arg Leu Arg Leu
 235 240 245
 Lys Gln Met Gln Glu Glu Phe Gln Glu His Glu Ala Gln Leu Leu Ser
 250 255 260 265
 Arg Ala Lys Pro Glu Asp Arg Glu Ser Leu Lys Ser Ala Cys Val Val
 270 275 280
 Cys Leu Ser Ser Phe Lys Ser Cys Val Phe Leu Glu Cys Gly His Val
 285 290 295
 Cys Ser Cys Thr Glu Cys Tyr Arg Ala Leu Pro Glu Pro Lys Lys Cys
 300 305 310
 Pro Ile Cys Arg Gln Ala Ile Thr Arg Val Ile Pro Leu Tyr Asn Ser
 315 320 325

<210> 106

<211> 385

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -184...-1

<400> 106

Met Trp Thr Phe Ser Tyr Ile Gly Phe Pro Val Glu Leu Asn Thr Val
 -180 -175 -170
 Tyr Phe Ile Gly Ala His Lys Ile Pro Asn Ala Asn Met Asn Glu Asp
 -165 -160 -155
 Gly Pro Ser Met Ser Val Asn Phe Thr Ser Pro Gly Cys Leu Asp His
 -150 -145 -140
 Ile Met Lys Tyr Lys Lys Lys Cys Val Lys Ala Gly Ser Leu Trp Asp
 -135 -130 -125
 Pro Asn Ile Thr Ala Cys Lys Lys Asn Glu Glu Thr Val Glu Val Asn
 -120 -115 -110 -105
 Phe Thr Thr Thr Pro Leu Gly Asn Arg Tyr Met Ala Leu Ile Gln His
 -100 -95 -90
 Ser Thr Ile Ile Gly Phe Ser Gln Val Phe Glu Pro His Gln Lys Lys
 -85 -80 -75
 Gln Thr Arg Ala Ser Val Val Ile Pro Val Thr Gly Asp Ser Glu Gly
 -70 -65 -60
 Ala Thr Val Gln Leu Thr Pro Tyr Phe Pro Thr Cys Gly Ser Asp Cys

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-55          -50          -45
Ile Arg His Lys Gly Thr Val Val Leu Cys Pro Gln Thr Gly Val Pro
-40          -35          -30          -25
Phe Pro Leu Asp Asn Asn Lys Ser Lys Pro Gly Gly Trp Leu Pro Leu
          -20          -15          -10
Leu Leu Leu Ser Leu Leu Val Ala Thr Trp Val Leu Val Ala Gly Ile
          -5          1          5
Tyr Leu Met Trp Arg His Glu Arg Ile Lys Lys Thr Ser Phe Ser Thr
    10          15          20
Thr Thr Leu Leu Pro Pro Ile Lys Val Leu Val Val Tyr Pro Ser Glu
25          30          35          40
Ile Cys Phe His His Thr Ile Cys Tyr Phe Thr Glu Phe Leu Gln Asn
          45          50          55
His Cys Arg Ser Glu Val Ile Leu Glu Lys Trp Gln Lys Lys Lys Ile
          60          65          70
Ala Glu Met Gly Pro Val Gln Trp Leu Ala Thr Gln Lys Lys Ala Ala
          75          80          85
Asp Lys Val Val Phe Leu Leu Ser Asn Asp Val Asn Ser Val Cys Asp
    90          95          100
Gly Thr Cys Gly Lys Ser Glu Gly Ser Pro Ser Glu Asn Ser Gln Asp
105          110          115          120
Leu Phe Pro Leu Ala Phe Asn Leu Phe Cys Ser Asp Leu Arg Ser Gln
          125          130          135
Ile His Leu His Lys Tyr Val Val Val Tyr Phe Arg Glu Ile Asp Thr
          140          145          150
Lys Asp Asp Tyr Asn Ala Leu Ser Val Cys Pro Lys Tyr His Leu Met
          155          160          165
Lys Asp Ala Thr Ala Phe Cys Ala Glu Leu Leu His Val Lys Gln Gln
          170          175          180
Val Ser Ala Gly Lys Arg Ser Gln Ala Cys His Asp Gly Cys Cys Ser
185          190          195          200
Leu

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<210> 107

<211> 69

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -23...-1

<400> 107

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Met Asn Leu Met Trp Thr Leu Leu Leu Phe Leu Leu Leu Asp Val Thr
      -20              -15              -10
Val Phe Ile Pro Ala Leu Pro Phe Ser Thr Arg His Ile Asp Asn Pro
      -5              1              5
Arg Ser Trp Val Pro Arg Gly His His Arg Tyr Cys Asp Val Met Met
10              15              20              25
Arg Arg Arg Trp Leu Ile Tyr Arg Gly Lys Cys Glu Gln Ile His Thr
      30              35              40
Phe Ile His Arg Ile
      45

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<210> 108

<211> 108

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -49...-1

<400> 108

```

Met Asn Lys Thr His Lys Asp Cys Ser Ser Pro Gln Tyr Ser Ile Tyr
      -45              -40              -35
Asn Ile Leu Asn Glu Leu Pro Thr Arg Pro Ile Ile Leu Ser Cys Ser
      -30              -25              -20
Gln Ile Ser Cys Leu Leu Leu Val Ser Thr Trp Ser Ala Asp Leu Met
      -15              -10              -5
Ser Tyr Arg Pro Val Thr Lys Pro Ser Gln Arg Cys Thr Ser Pro Ala
      1              5              10              15
Gln Ser Met Thr Val Asn Leu Thr Lys Asp Val Gly Phe Tyr Glu Asp
      20              25              30
Thr Gln Ser Ile Arg Ile Thr Leu Ser Glu Ile Ser Gln Ala Gln Lys
      35              40              45
Asp Thr Tyr Phe Ile Ile Ser Cys Ile Cys Gly Ile
      50              55

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<210> 109

<211> 108

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -28...-1

<400> 109

Met Tyr Phe His Phe Leu Gly Ala Gly Ala Ile Leu Ile Pro Arg Leu
 -25 -20 -15
 Asp Ile Val Ile Ser Phe Val Gly Ala Val Ser Ser Ser Thr Leu Ala
 -10 -5 1
 Leu Ile Leu Pro Pro Leu Val Glu Ile Leu Thr Phe Ser Lys Glu His
 5 10 15 20
 Tyr Asn Ile Trp Met Val Leu Lys Asn Ile Ser Ile Ala Phe Thr Gly
 25 30 35
 Val Val Gly Phe Leu Leu Gly Thr Tyr Ile Thr Val Glu Glu Ile Ile
 40 45 50
 Tyr Pro Thr Pro Lys Val Val Ala Gly Thr Pro Gln Ser Pro Phe Leu
 55 60 65
 Asn Leu Asn Ser Thr Cys Leu Thr Ser Gly Leu Lys
 70 75 80

<210> 110

<211> 125

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -37...-1

<400> 110

Met Val Cys Glu Asp Ala Pro Ser Phe Gln Met Ala Trp Glu Ser Gln
 -35 -30 -25
 Met Ala Trp Glu Arg Gly Pro Ala Leu Leu Cys Cys Val Leu Ser Ala
 -20 -15 -10
 Ser Gln Leu Ser Ser Gln Asp Gln Asp Pro Leu Gly His Ile Lys Ser
 -5 1 5 10
 Leu Leu Tyr Pro Phe Gly Phe Pro Val Glu Leu Pro Arg Pro Gly Pro
 15 20 25
 Thr Gly Ala Tyr Lys Lys Val Lys Asn Gln Asn Gln Thr Thr Ser Ser
 30 35 40
 Glu Leu Leu Arg Lys Gln Thr Ser His Phe Asn Gln Arg Gly His Arg
 45 50 55

160

Ala Arg Ser Lys Leu Leu Ala Ser Arg Gln Ile Pro Asp Arg Thr Phe.
 60 65 70 75
 Lys Cys Gly Lys Trp Leu Pro Gln Val Pro Ser Pro Val
 80 85

<210> 111

<211> 169

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -88...-1

<400> 111

Met Lys Gly Gly Ile Ser Asn Val Trp Phe Asp Arg Phe Lys Ile Thr
 -85 -80 -75
 Asn Asp Cys Pro Glu His Leu Glu Ser Ile Asp Val Met Cys Gln Val
 -70 -65 -60
 Leu Thr Asp Leu Ile Asp Glu Glu Val Lys Ser Gly Ile Lys Lys Asn
 -55 -50 -45
 Arg Ile Leu Ile Gly Gly Phe Ser Met Gly Gly Cys Met Ala Met His
 -40 -35 -30 -25
 Leu Ala Tyr Arg Asn His Gln Asp Val Ala Gly Val Phe Ala Leu Ser
 -20 -15 -10
 Ser Phe Leu Asn Lys Ala Ser Ala Val Tyr Gln Ala Leu Gln Lys Ser
 -5 1 5
 Asn Gly Val Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu
 10 15 20
 Leu Val Leu His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser
 25 30 35 40
 Leu Gly Val Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu
 45 50 55
 Leu Ser Lys Thr Glu Leu Asp Ile Leu Lys Leu Trp Ile Leu Thr Lys
 60 65 70
 Leu Pro Gly Glu Met Glu Lys Gln Lys
 75 80

<210> 112

<211> 82

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -56...-1

<400> 112

Met Lys Ala Val Trp His Phe Cys Leu Ser His Lys Ser Ser Leu Val
 -55 -50 -45
 Ile Val Leu Lys Thr Ala Gly Trp Ile Pro Gln Ala Gly Thr Leu Ile
 -40 -35 -30 -25
 Pro Gly Ser Arg Glu Glu Ser Arg Ser Asp Ser Gln Met Ile Met Leu
 -20 -15 -10
 Val Cys Phe Asn Leu Ser Arg Gly Cys Leu Lys Lys Val Phe Ile Ile
 -5 1 5
 Ser Val Leu Pro Asp Pro Glu Thr Ile Leu Leu Gly Lys Thr Val Gly
 10 15 20
 Ile Ala
 25

<210> 113

<211> 251

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -20...-1

<400> 113

Met Asp Lys Val Gln Ser Gly Phe Leu Ile Leu Phe Leu Phe Leu Met
 -20 -15 -10 -5
 Glu Cys Gln Leu His Leu Cys Leu Pro Tyr Ala Asp Gly Leu His Pro
 1 5 10
 Thr Gly Asn Ile Thr Gly Leu Pro Gly Ser Phe Asn His Trp Phe Tyr
 15 20 25
 Val Thr Gln Gly Glu Leu Lys Ser Cys Phe Arg Gly Asp Lys Lys Lys
 30 35 40
 Val Ile Thr Phe His Arg Lys Lys Phe Ser Phe Gln Gly Ser Lys Arg
 45 50 55 60
 Ser Gln Pro Pro Arg Asn Ile Thr Lys Glu Pro Lys Val Phe Phe His
 65 70 75
 Lys Thr Gln Leu Pro Gly Ile Gln Gly Ala Ala Ser Arg Ser Thr Ala

162

80	85	90
Ala Ser Pro Thr Asn Pro Met Lys Phe Leu Arg Asn Lys Ala Ile Ile		
95	100	105
Arg His Arg Pro Ala Leu Val Lys Val Ile Leu Ile Ser Ser Val Ala		
110	115	120
Phe Ser Ile Ala Leu Ile Cys Gly Met Ala Ile Ser Tyr Met Ile Tyr		
125	130	135
Arg Leu Ala Gln Ala Glu Glu Arg Gln Gln Leu Glu Ser Leu Tyr Lys		
145	150	155
Asn Leu Arg Ile Pro Leu Leu Gly Asp Glu Glu Glu Gly Ser Glu Asp		
160	165	170
Glu Gly Glu Ser Thr His Leu Leu Pro Lys Asn Glu Asn Glu Leu Glu		
175	180	185
Lys Phe Ile His Ser Val Ile Ile Ser Lys Arg Ser Lys Asn Ile Lys		
190	195	200
Lys Lys Leu Lys Glu Glu Gln Asn Ser Val Thr Glu Asn Lys Thr Lys		
205	210	215
Asn Ala Ser His Asn Gly Lys Met Glu Asp Leu		
225	230	

<210> 114

<211> 305

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -34...-1

<400> 114

Met Ser Phe Leu Arg Ile Thr Pro Ser Thr His Ser Ser Val Ser Ser		
-30	-25	-20
Gly Leu Leu Arg Leu Ser Ile Phe Leu Leu Leu Ser Phe Pro Asp Ser		
-15	-10	-5
Asn Gly Lys Ala Ile Trp Thr Ala His Leu Asn Ile Thr Phe Gln Val		
1	5	10
Gly Asn Glu Ile Thr Ser Glu Leu Gly Glu Ser Gly Val Phe Gly Asn		
15	20	25
His Ser Pro Leu Glu Arg Val Ser Gly Val Val Ala Leu Pro Glu Glu		
35	40	45
Trp Asn Gln Asn Ala Cys His Pro Leu Thr Asn Phe Ser Arg Pro Lys		
50	55	60

163

Gln Ala Asp Ser Trp Leu Ala Leu Ile Glu Arg Gly Gly Cys Thr Phe
 65 70 75
 Thr His Lys Ile Asn Val Ala Ala Glu Lys Gly Ala Asn Gly Val Ile
 80 85 90
 Ile Tyr Asn Tyr Gln Gly Thr Gly Ser Lys Val Phe Pro Met Ser His
 95 100 105 110
 Gln Gly Thr Glu Asn Ile Val Ala Val Met Ile Ser Asn Leu Lys Gly
 115 120 125
 Met Glu Ile Leu His Ser Ile Gln Lys Gly Val Tyr Val Thr Val Ile
 130 135 140
 Ile Glu Val Gly Arg Met His Met Gln Trp Val Ser His Tyr Ile Met
 145 150 155
 Tyr Leu Phe Thr Phe Leu Ala Ala Thr Ile Ala Tyr Phe Tyr Leu Asp
 160 165 170
 Cys Val Trp Arg Leu Thr Pro Arg Val Pro Asn Ser Phe Thr Arg Arg
 175 180 185 190
 Arg Ser Gln Ile Lys Thr Asp Val Lys Lys Ala Ile Asp Gln Leu Gln
 195 200 205
 Leu Arg Val Leu Lys Glu Gly Asp Glu Glu Leu Asp Leu Asn Glu Asp
 210 215 220
 Asn Cys Val Val Cys Phe Asp Thr Tyr Lys Pro Gln Asp Val Val Arg
 225 230 235
 Ile Leu Thr Cys Lys His Phe Phe His Lys Ala Cys Ile Asp Pro Trp
 240 245 250
 Leu Leu Ala His Arg Thr Cys Pro Met Cys Lys Cys Asp Ile Leu Lys
 255 260 265 270
 Thr

<210> 115

<211> 61

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -42...-1

<400> 115

Met Thr Asp Leu Asp Leu Met Ile Asn Phe Thr Phe Pro Ile Gln Trp
 -40 -35 -30
 Val Asn Gln Asn Arg Met Ala Tyr Tyr Ser Leu Lys Pro Leu Leu Pro
 -25 -20 -15

164

Cys Ser Ser Val Leu Thr Cys Gly Gln Ala Ser Gln Asp Leu Leu Thr
 -10 -5 1 5
 Ser Ala Thr Ser Val Thr Gly Met Glu Lys Ile Glu Ala
 10 15

<210> 116

<211> 113

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -15...-1

<400> 116

Met Asn Phe Tyr Leu Leu Leu Ala Ser Ser Ile Leu Cys Ala Leu Ile
 -15 -10 -5 1
 Val Phe Trp Lys Tyr Arg Arg Phe Gln Arg Asn Thr Gly Glu Met Ser
 5 10 15
 Ser Asn Ser Thr Ala Leu Ala Leu Val Arg Pro Ser Ser Ser Gly Leu
 20 25 30
 Ile Asn Ser Asn Thr Asp Asn Asn Leu Ala Val Tyr Asp Leu Ser Arg
 35 40 45
 Asp Ile Leu Asn Asn Phe Pro His Ser Ile Ala Arg Gln Lys Arg Ile
 50 55 60 65
 Leu Val Asn Leu Ser Met Val Glu Asn Lys Leu Val Glu Leu Glu His
 70 75 80
 Thr Leu Leu Ser Lys Gly Phe Arg Gly Ala Ser Pro His Arg Lys Ser
 85 90 95
 Thr

<210> 117

<211> 101

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -30...-1

<400> 117

Met Glu Arg Pro Arg Ser Pro Gln Cys Ser Ala Pro Ala Ser Ala Ser

165

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-30          -25          -20          -15
Ala Ser Val Thr Leu Ala Gln Leu Leu Gln Leu Val Gln Gln Gly Gln
          -10          -5          1
Glu Leu Pro Gly Leu Glu Lys Arg His Ile Ala Ala Ile His Gly Glu
      5          10          15
Pro Thr Ala Ser Arg Leu Pro Arg Arg Pro Lys Pro Trp Glu Ala Ala
    20          25          30
Ala Leu Ala Glu Ser Leu Pro Pro Pro Thr Leu Arg Ile Gly Thr Ala
35          40          45          50
Pro Ala Glu Pro Gly Leu Val Glu Ala Ala Thr Ala Pro Ser Ser Trp
      55          60          65
His Thr Val Gly Pro
          70

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<210> 118

<211> 97

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -90...-1

<220>

<221> UNSURE

<222> -39

<223> Xaa = His,Gln

<400> 118

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Met Asn Gln Glu Asn Pro Pro Pro Tyr Pro Gly Pro Gly Pro Thr Ala
-90          -85          -80          -75
Pro Tyr Pro Pro Tyr Pro Pro Gln Pro Met Gly Pro Gly Pro Met Gly
          -70          -65          -60
Gly Pro Tyr Pro Pro Pro Gln Gly Tyr Pro Tyr Gln Gly Tyr Leu Gln
          -55          -50          -45
Tyr Gly Trp Xaa Gly Gly Pro Gln Glu Pro Pro Lys Thr Thr Val Tyr
          -40          -35          -30
Val Val Glu Asp Gln Arg Arg Asp Glu Leu Gly Pro Ser Thr Cys Leu
          -25          -20          -15
Thr Ala Cys Trp Thr Ala Leu Cys Cys Cys Cys Leu Trp Asp Met Leu
-10          -5          1          5
Thr

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<210> 119
 <211> 101
 <212> PRT
 <213> Homo Sapiens

<220>
 <221> SIGNAL
 <222> -25...-1

<400> 119
 Met Val Asp Arg Glu Leu Ala Asp Ile His Glu Asp Ala Lys Thr Cys
 -25 -20 -15 -10
 Leu Val Leu Cys Ser Arg Val Leu Ser Val Ile Ser Val Lys Glu Ile
 -5 1 5
 Lys Thr Gln Leu Ser Leu Gly Arg His Pro Ile Ile Ser Asn Trp Phe
 10 15 20
 Asp Tyr Ile Pro Ser Thr Arg Tyr Lys Asp Pro Cys Glu Leu Leu His
 25 30 35
 Leu Cys Arg Leu Thr Ile Arg Asn Gln Leu Leu Thr Asn Asn Met Leu
 40 45 50 55
 Pro Asp Gly Ile Phe Ser Leu Leu Ile Pro Ala Arg Leu Gln Asn Tyr
 60 65 70
 Leu Asn Leu Glu Ile
 75

<210> 120
 <211> 152
 <212> PRT
 <213> Homo Sapiens

<220>
 <221> SIGNAL
 <222> -101...-1

<400> 120
 Met Asp Asn Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser
 -100 -95 -90
 Val Lys Gly His Val Lys Met Leu Arg Leu Ala Leu Thr Val Thr Ser
 -85 -80 -75 -70
 Met Thr Phe Phe Ile Ile Ala Gln Ala Pro Glu Pro Tyr Ile Val Ile
 -65 -60 -55

167

Thr Gly Phe Glu Val Thr Val Ile Leu Phe Phe Ile Leu Leu Tyr Val
 -50 -45 -40
 Leu Arg Leu Asp Arg Leu Met Lys Trp Leu Phe Trp Pro Leu Leu Asp
 -35 -30 -25
 Ile Ile Asn Ser Leu Val Thr Thr Val Phe Met Leu Ile Val Ser Val
 -20 -15 -10
 Leu Ala Leu Ile Pro Glu Thr Thr Thr Leu Thr Val Gly Gly Gly Val
 -5 1 5 10
 Phe Ala Leu Val Thr Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile
 15 20 25
 Tyr Arg Lys Leu Leu Phe Asn Pro Ser Gly Pro Tyr Gln Lys Lys Pro
 30 35 40
 Val His Glu Lys Lys Glu Val Leu
 45 50

<210> 121

<211> 209

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -86...-1

<400> 121

Met Leu Ser Pro Thr Phe Val Leu Trp Asp Val Gly Tyr Pro Leu Tyr
 -85 -80 -75
 Thr Tyr Gly Ser Ile Cys Ile Ile Ala Leu Ile Ile Trp Gln Val Lys
 -70 -65 -60 -55
 Lys Ser Cys Gln Lys Leu Ser Leu Val Pro Asn Arg Ser Cys Cys Arg
 -50 -45 -40
 Cys His Arg Arg Val Gln Gln Lys Ser Gly Asp Arg Thr Ser Arg Ala
 -35 -30 -25
 Arg Arg Thr Ser Gln Glu Glu Ala Glu Lys Leu Trp Lys Leu Leu Phe
 -20 -15 -10
 Leu Met Lys Ser Gln Gly Trp Ile Pro Gln Glu Gly Ser Val Arg Arg
 -5 1 5 10
 Ile Leu Cys Ala Asp Pro Cys Cys Gln Ile Cys Asn Val Met Ala Leu
 15 20 25
 Glu Ile Lys Gln Leu Leu Ala Glu Ala Pro Glu Val Gly Leu Asp Asn
 30 35 40
 Lys Met Lys Leu Phe Leu His Trp Ile Asn Pro Glu Met Lys Asp Arg

168

45 50 55
 Arg His Glu Glu Ser Ile Leu Leu Ser Lys Ala Glu Thr Val Thr Gln
 60 65 70
 Asp Arg Thr Lys Asn Ile Glu Lys Ser Pro Thr Val Thr Lys Asp His
 75 80 85 90
 Val Trp Gly Ala Thr Thr Gln Lys Thr Thr Glu Asp Pro Glu Ala Gln
 95 100 105
 Pro Pro Ser Thr Glu Glu Glu Gly Leu Ile Phe Cys Asp Ala Pro Ser
 110 115 120
 Ala

<210> 122

<211> 89

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -21...-1

<400> 122

Met Gly Ser Cys Ser Gly Arg Cys Ala Leu Val Val Leu Cys Ala Phe
 -20 -15 -10
 Gln Leu Val Ala Ala Leu Glu Arg Gln Val Phe Asp Phe Leu Gly Tyr
 -5 1 5 10
 Gln Trp Ala Pro Ile Leu Ala Asn Phe Val His Ile Ile Ile Val Ile
 15 20 25
 Leu Gly Leu Phe Gly Thr Ile Gln Tyr Arg Leu Arg Tyr Val Met Cys
 30 35 40
 Thr Arg Cys Gly Gln Pro Ser Gly Ser Pro Gly Thr Ser Ser Ser Ser
 45 50 55
 Ala Ser Thr Trp Lys Ser Val Ala Ser
 60 65

<210> 123

<211> 66

<212> PRT

<213> Homo Sapiens

<220>

<221> SIGNAL

<222> -19...-1

<400> 123

Met Lys Pro Leu Leu Val Val Phe Val Phe Leu Phe Leu Trp Asp Pro
 -15 -10 -5
 Val Leu Ala Gly Ile Asn Ser Leu Ser Ser Glu Met His Lys Lys Cys
 1 5 10
 Tyr Lys Asn Gly Ile Cys Arg Leu Glu Cys Tyr Glu Ser Glu Met Leu
 15 20 25
 Val Ala Tyr Cys Met Phe Gln Leu Glu Cys Cys Val Lys Gly Asn Pro
 30 35 40 45
 Ala Pro

<210> 124

<211> 249

<212> PRT

<213> Homo Sapiens

<400> 124

Met Leu Gln Leu Trp Lys Leu Val Leu Leu Cys Gly Val Leu Thr Gly
 1 5 10 15
 Thr Ser Glu Ser Leu Leu Asp Asn Leu Gly Asn Asp Leu Ser Asn Val
 20 25 30
 Val Asp Lys Leu Glu Pro Val Leu His Glu Gly Leu Glu Thr Val Asp
 35 40 45
 Asn Thr Leu Lys Gly Ile Leu Glu Lys Leu Lys Val Asp Leu Gly Val
 50 55 60
 Leu Gln Lys Ser Ser Ala Trp Gln Leu Ala Lys Gln Lys Ala Gln Glu
 65 70 75 80
 Ala Glu Lys Leu Leu Asn Asn Val Ile Ser Lys Leu Leu Pro Thr Asn
 85 90 95
 Thr Asp Ile Phe Gly Leu Lys Ile Ser Asn Ser Leu Ile Leu Asp Val
 100 105 110
 Lys Ala Glu Pro Ile Asp Asp Gly Lys Gly Leu Asn Leu Ser Phe Pro
 115 120 125
 Val Thr Ala Asn Val Thr Val Ala Gly Pro Ile Ile Gly Gln Ile Ile
 130 135 140
 Asn Leu Lys Ala Ser Leu Asp Leu Leu Thr Ala Val Thr Ile Glu Thr
 145 150 155 160
 Asp Pro Gln Thr His Gln Pro Val Ala Val Leu Gly Glu Cys Ala Ser
 165 170 175
 Asp Pro Thr Ser Ile Ser Leu Ser Leu Leu Asp Lys His Ser Gln Ile
 180 185 190

170

Ile Asn Lys Phe Val Asn Ser Val Ile Asn Thr Leu Lys Ser Thr Val
 195 200 205
 Ser Ser Leu Leu Gln Lys Glu Ile Cys Pro Leu Ile Arg Ile Phe Ile
 210 215 220
 His Ser Leu Asp Val Asn Val Ile Gln Gln Val Val Asp Asn Pro Gln
 225 230 235 240
 His Lys Thr Gln Leu Gln Thr Leu Ile
 245

<210> 125

<211> 382

<212> PRT

<213> Homo Sapiens

<400> 125

Met Gly Leu Leu Leu Pro Leu Ala Leu Cys Ile Leu Val Leu Cys Cys
 1 5 10 15
 Gly Ala Met Ser Pro Pro Gln Leu Ala Leu Asn Pro Ser Ala Leu Leu
 20 25 30
 Ser Arg Gly Cys Asn Asp Ser Asp Val Leu Ala Val Ala Gly Phe Ala
 35 40 45
 Leu Arg Asp Ile Asn Lys Asp Arg Lys Asp Gly Tyr Val Leu Arg Leu
 50 55 60
 Asn Arg Val Asn Asp Ala Gln Glu Tyr Arg Arg Gly Gly Leu Gly Ser
 65 70 75 80
 Leu Phe Tyr Leu Thr Leu Asp Val Leu Glu Thr Asp Cys His Val Leu
 85 90 95
 Arg Lys Lys Ala Trp Gln Asp Cys Gly Met Arg Ile Phe Phe Glu Ser
 100 105 110
 Val Tyr Gly Gln Cys Lys Ala Ile Phe Tyr Met Asn Asn Pro Ser Arg
 115 120 125
 Val Leu Tyr Leu Ala Ala Tyr Asn Cys Thr Leu Arg Pro Val Ser Lys
 130 135 140
 Lys Lys Ile Tyr Met Thr Cys Pro Asp Cys Pro Ser Ser Ile Pro Thr
 145 150 155 160
 Asp Ser Ser Asn His Gln Val Leu Glu Ala Ala Thr Glu Ser Leu Ala
 165 170 175
 Lys Tyr Asn Asn Glu Asn Thr Ser Lys Gln Tyr Ser Leu Phe Lys Val
 180 185 190
 Thr Arg Ala Ser Ser Gln Trp Val Val Gly Pro Ser Tyr Phe Val Glu
 195 200 205
 Tyr Leu Ile Lys Glu Ser Pro Cys Thr Lys Ser Gln Ala Ser Ser Cys

171

210 215 220
 Ser Leu Gln Ser Ser Asp Ser Val Pro Val Gly Leu Cys Lys Gly Ser
 225 230 235 240
 Leu Thr Arg Thr His Trp Glu Lys Phe Val Ser Val Thr Cys Asp Phe
 245 250 255
 Phe Glu Ser Gln Ala Pro Ala Thr Gly Ser Glu Asn Ser Ala Val Asn
 260 265 270
 Gln Lys Pro Thr Asn Leu Pro Lys Val Glu Glu Ser Gln Gln Lys Asn
 275 280 285
 Thr Pro Pro Thr Asp Ser Pro Ser Lys Ala Gly Pro Arg Gly Ser Val
 290 295 300
 Gln Tyr Leu Pro Asp Leu Asp Asp Lys Asn Ser Gln Glu Lys Gly Pro
 305 310 315 320
 Gln Glu Ala Phe Pro Val His Leu Asp Leu Thr Thr Asn Pro Gln Gly
 325 330 335
 Glu Thr Leu Asp Ile Ser Phe Leu Phe Leu Glu Pro Met Glu Glu Lys
 340 345 350
 Leu Val Val Leu Pro Phe Pro Lys Glu Lys Ala Arg Thr Ala Glu Cys
 355 360 365
 Pro Gly Pro Ala Gln Asn Ala Ser Pro Leu Val Leu Pro Pro
 370 375 380

<210> 126

<211> 302

<212> PRT

<213> Mus Musculus

<400> 126

Met Lys Ala Pro Gly Arg Leu Leu Leu Leu Thr Leu Cys Ile Leu Thr
 1 5 10 15
 Phe Ser Ala Val Cys Val Phe Leu Cys Cys Trp Ala Cys Leu Pro Leu
 20 25 30
 Cys Leu Ala Thr Cys Leu Asp Arg His Leu Pro Ala Ala Pro Arg Ser
 35 40 45
 Thr Val Pro Gly Pro Leu His Phe Ser Gly Tyr Ser Ser Val Pro Asp
 50 55 60
 Gly Lys Pro Leu Ile Arg Glu Leu Cys His Ser Cys Ala Val Val Ser
 65 70 75 80
 Ser Ser Gly Gln Met Leu Gly Ser Gly Leu Gly Ala Gln Ile Asp Gly
 85 90 95
 Ala Glu Cys Val Leu Arg Met Asn Gln Ala Pro Thr Val Gly Phe Glu
 100 105 110

172

Glu Asp Val Gly Gln Arg Ser Thr Leu Arg Val Ile Ser His Thr Ser
 115 120 125
 Val Pro Leu Leu Leu Arg Asn Tyr Ser His Tyr Phe Gln His Ala Arg
 130 135 140
 Asp Thr Leu Tyr Val Val Trp Gly Gln Gly Arg His Met Asp Arg Val
 145 150 155 160
 Leu Gly Gly Arg Thr Tyr Arg Thr Leu Leu Gln Leu Thr Arg Met Tyr
 165 170 175
 Pro Gly Leu Gln Val Tyr Thr Phe Thr Glu Arg Met Met Ala Tyr Cys
 180 185 190
 Asp Gln Ile Phe Gln Asp Glu Thr Gly Lys Asn Arg Arg Gln Ser Gly
 195 200 205
 Ser Phe Leu Ser Thr Gly Trp Phe Thr Met Ile Leu Ala Leu Glu Leu
 210 215 220
 Cys Glu Glu Ile Val Val Tyr Gly Met Val Ser Asp Ser Tyr Cys Ser
 225 230 235 240
 Glu Lys Ser Pro Arg Ser Val Pro Tyr His Tyr Phe Glu Lys Gly Arg
 245 250 255
 Leu Asp Glu Cys Gln Met Tyr Arg Leu His Glu Gln Ala Pro Arg Ser
 260 265 270
 Ala His Arg Phe Ile Thr Glu Lys Ala Val Phe Ser Arg Trp Ala Lys
 275 280 285
 Lys Arg Pro Ile Val Phe Ala His Pro Ser Trp Arg Ala Lys
 290 295 300

<210> 127

<211> 9

<212> DNA

<213> Artificial Sequence

<400> 127

tgtcagttg

9

<210> 128

<211> 10

<212> DNA

<213> Artificial Sequence

<400> 128

cccaactgac

10

<210> 129

<211> 11
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<400> 129
aatagaatta g

11

<210> 130
<211> 11
<212> DNA
<213> Artificial Sequence

<400> 130
aactaaatta g

11

<210> 131
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<212> DNA
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<400> 131
gcacacctca g

11

<210> 132
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<400> 132
agataaatcc a

11

<210> 133
<211> 9
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<400> 133
cttcagttg

9

<210> 134
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<213> Artificial Sequence

<400> 134

ttgtagatag gaca

14

<210> 135

<211> 11

<212> DNA

<213> Artificial Sequence

<400> 135

agataggaca t

11

<210> 136

<211> 16

<212> DNA

<213> Artificial Sequence

<400> 136

cataacagat ggtaag

16

<210> 137

<211> 16

<212> DNA

<213> Artificial Sequence

<400> 137

cataacagat ggtaag

16

<210> 138

<211> 16

<212> DNA

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<400> 138

cataacagat ggtaag

16

<210> 139

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accatctggt	10
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tcaagataaa gta	13
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agttgggaat tcc	13
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agttgggaat tc	12
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<211> 10	
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<400> 143	
tggaattcc	10
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<400> 144	
tcagtgatat ggca	14

<210> 145
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<400> 145
taaaacaaaa ca

12

<210> 146
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<213> Artificial Sequence

<400> 146
tttagcgc

8

<210> 147
<211> 8
<212> DNA
<213> Artificial Sequence

<400> 147
tgagggga

8

<210> 148
<211> 11
<212> DNA
<213> Artificial Sequence

<400> 148
ggaccaatca t

11

<210> 149
<211> 8
<212> DNA
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<400> 149
cctgggga

8

<210> 150

<211> 9
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<400> 150
tgaccgttg

9

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<400> 151
tccaacggt

9

<210> 152
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<400> 152
ttcctggaa

9

<210> 153
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<400> 153
ttccaggaa

9

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<400> 154
ttggggga

8

<210> 155
<211> 12
<212> DNA

<213> Artificial Sequence

<400> 155

gaatgggatt tc

12

<210> 156

<211> 12

<212> DNA

<213> Artificial Sequence

<400> 156

gaaaacaaaa ca

12

<210> 157

<211> 8

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<213> Artificial Sequence

<400> 157

gaagggga

8

<210> 158

<211> 10

<212> DNA

<213> Artificial Sequence

<400> 158

agcatctgcc

10

<210> 159

<211> 11

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<213> Artificial Sequence

<400> 159

tcccaccttc c

11

<210> 160

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gaggcaatta t	11
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agagggga	8
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ggactcacgt gctgct	16
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actcacgtgc tg	12
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actcacgtgc tg	12
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cagcacgtga gt	12

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<400> 166
accatctgtt

10

<210> 167
<211> 12
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<400> 167
cagcacgtga gt

12

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cagcacgtga gt

12

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<400> 169
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<400> 170
gcacgtga

8

<210> 171

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<400> 171
catgggga

8

<210> 172
<211> 14
<212> DNA
<213> Artificial Sequence

<400> 172
ctctccggaa gcct

14

<210> 173
<211> 10
<212> DNA
<213> Artificial Sequence

<400> 173
tccggaagcc

10

<210> 174
<211> 11
<212> DNA
<213> Artificial Sequence

<400> 174
agtgactgaa c

11

<210> 175
<211> 11
<212> DNA
<213> Artificial Sequence

<400> 175
agtgactgaa c

11

<210> 176
<211> 9
<212> DNA

WO 00/37491

PCT/IB99/02058

182

<213> Artificial Sequence

<400> 176

tgtggtctc

9